TITLE OF THE INVENTION

ALPHA-CONOTOXIN PEPTIDES

CROSS-REFERENCE TO RELATED APPLICATION

The present application is related to U.S. provisional patent application Serial No. 60/118,381, filed 29 January 1999, incorporated herein by reference.

This invention was made with Government support under Grant No. PO1 GM48677 awarded by the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland. The United States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

The invention relates to relatively short peptides (termed α-conotoxins herein), about 10-30 residues in length, which are naturally available in minute amounts in the venom of the cone snails or analogous to the naturally available peptides, and which preferably include two disulfide bonds.

The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference, and for convenience are referenced in the following text by author and date and are listed alphabetically by author in the appended bibliography.

The predatory cone snails (*Conus*) have developed a unique biological strategy. Their venom contains relatively small peptides that are targeted to various neuromuscular receptors and may be equivalent in their pharmacological diversity to the alkaloids of plants or secondary metabolites of microorganisms. Many of these peptides are among the smallest nucleic acid-encoded translation products having defined conformations, and as such, they are somewhat unusual. Peptides in this size range normally equilibrate among many conformations. Proteins having a fixed conformation are generally much larger.

The cone snails that produce these peptides are a large genus of venomous gastropods comprising approximately 500 species. All cone snail species are predators that inject venom to capture prey, and the spectrum of animals that the genus as a whole can envenomate is broad. A wide variety of hunting strategies are used, however, every *Conus* species uses fundamentally the same basic pattern of envenomation.

Several peptides isolated from *Conus* venoms have been characterized. These include the α-, μ- and ω-conotoxins which target nicotinic acetylcholine receptors, muscle sodium channels,

and neuronal calcium channels, respectively (Olivera et al., 1985). Conopressins, which are vasopressin analogs, have also been identified (Cruz et al.. 1987). In addition, peptides named conantokins have been isolated from *Conus geographus* and *Conus tulipa* (Mena et al., 1990; Haack et al., 1990).

The α-conotoxins are small peptides highly specific for neuromuscular junction nicotinic acetylcholine receptors (Gray et al., 1981; Marshall and Harvey, 1990; Blount et al., 1992; Jacobsen et al., 1997) or highly specific for neuronal nicotinic acetylcholine receptors (Fainzilber et al., 1994; Johnson et al., 1995; Cartier et al., 1996; Luo et al., 1998). The α-conotoxins with specificity for neuromuscular junction nicotinic acetylcholine receptors are used as neuromuscular blocking agents for use in conjunction with surgery, as disclosed in U.S. patent application Serial No. 09/_____, filed 21 January 2000 (Attorney Docket No. 2314-178.A) and international patent application No. PCT/US00/_____, filed 21 January 2000 (Attorney Docket No. 2314-138.PCT), each incorporated by reference herein. Additional α-conotoxins and uses for them have been described in U.S. Patent Nos. 4,447,356 (Olivera et al., 1984); 5,432,155; 5,514,774; each incorporated herein by reference.

Additional uses for α-conotoxins are described in U.S. Serial No. 09/219,446, filed 22 December 1998, incorporated herein by reference. In this application, α-conotoxins with specificity for neuronal nicotinic acetylcholine receptors are used for treating disorders regulated at neuronal nicotinic acetylcholine receptors. Such disorders include, but are not limited to, cardiovascular disorders, gastric motility disorders, urinary incontinence, nicotine addiction, mood disorders (such as bipolar disorder, unipolar depression, dysthymia and seasonal effective disorder) and small cell lung carcinoma, as well as the localization of small cell lung carcinoma.

It is desired to provide additional α-conotoxin peptides having uses as described herein.

SUMMARY OF THE INVENTION

The invention relates to relatively short peptides (termed α-conotoxins herein), about 10-30 residues in length, which are naturally available in minute amounts in the venom of the cone snails or analogous to the naturally available peptides, and which preferably include two disulfide bonds.

More specifically, the present invention is directed to α-conotoxin peptides having the general formula I:

~~Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-Cys-Cys-Xaa_6-Xaa_7-Xaa_8-Xaa_9-Cys-Xaa_{10}-Xaa_{11}-Xaa_{12}-Cys-~~ Xaa_{13} (SEQ ID NO1:), wherein ~~Xaa_1 is des-Xaa_1~~, Ile, Leu or Val; Xaa_2 is des-Xaa_2, Ala or Gly; Xaa_3 ~~is des-Xaa_3, Gly, Trp (D or L), neo-Trp, halo-Trp or any unnatural aromatic amino acid; Xaa_4 is des-~~

~~Xaa_4, Asp, Phe, Gly, Ala, Glu, γ-carboxy-Glu (Gla) or any unnatural aromatic amino acid; Xaa_5 is~~ Glu, Gla, Asp, Ala, Thr, Ser, Gly, Ile, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_6 is Ser, Thr, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_7 is Asp, Glu, Gla, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_8 is Ser, Thr, Asn, Ala, Gly, His, halo-His, Pro or hydroxy-Pro; Xaa_9 is Thr, Ser, Ala, Asp, Asn, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{10} is Gly, Ser, Thr, Ala, Asn, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{11} is Gln, Leu, His, halo-His, Trp (D or L), halo-Trp, neo-Trp, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid or any unnatural aromatic amino acid; Xaa_{12} is Asn, His, halo-His, Ile, Leu, Val, Gln, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{13} is des-Xaa_{13}, Val, Ile, Leu, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid. The C-terminus may contain a free carboxyl group or an amide group. The halo is chlorine, bromine or iodine, preferably iodine for Tyr and His and preferably bromine for Trp. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic bioisoteric ~~amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.~~

More specifically, the present invention is directed to α-conotoxin peptides having the general formula II:

Xaa_1-Xaa_2-Xaa_3-Xaa_4-Cys-Cys-Xaa_5-Xaa_6-Xaa_7-Xaa_8-Cys-Xaa_9-Xaa_{10}-Xaa_{11}-Xaa_{12}-Xaa_{13}-Xaa_{14}-Cys-Xaa_{15}-Xaa_{16}-Xaa_{17} (SEQ ID NO:2), wherein Xaa_1 is des-Xaa_1, Asp, Glu or γ-carboxy-Glu (Gla); Xaa_2 is des-Xaa_2, Gln, Ala, Asp, Glu, Gla; Xaa_3 is des-Xaa_3, Gly, Ala, Asp, Glu, Gla, Pro or hydroxy-Pro; Xaa_4 is des-Xaa_4, Gly, Glu, Gla, Gln, Asp, Asn, Pro or hydroxy-Pro; Xaa_5 is Ser, Thr, Gly, Glu, Gla, Asn, Trp (D or L), neo-Trp, halo-Trp, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing

amino acid; Xaa_6 is Asp, Asn, His, halo-His, Thr, Ser, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_7 is Pro or hydroxy-Pro; Xaa_8 is Ala, Ser, Thr, Asp, Val, Ile, Pro, hydroxy-Pro, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_9 is Gly, Ile, Leu, Val, Ala, Thr, Ser, Pro, hydroxy-Pro, Phe, Trp (D or L), neo-Trp, halo-Trp, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid or any unnatural aromatic amino acid; Xaa_{10} is Ala, Asn, Phe, Pro, hydroxy-Pro, Glu, Gla, Gln, His, halo-His, Val, Ser, Thr, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{11} is Thr, Ser, His, halo-His, Leu, Ile, Val, Asn, Met, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{12} is Asn, Pro, hydroxy-Pro, Gln, Ser, Thr, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys N,N,N-trimethyl-Lys, any unnatural basic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{13} is des-Xaa_{13}, Gly, Thr, Ser, Pro, hydroxy-Pro, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{14} is des-Xaa_{14}, Ile, Val, Asp, Leu, Phe, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; and Xaa_{15} is des-Xaa_{15}, Gly, Ala, Met, Ser, Thr, Trp (D or L), neo-Trp, halo-Trp, any unnatural aromatic amino acid, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{16} is des-Xaa_{16}, Trp (D or L), neo-Trp, halo-Trp, any unnatural aromatic amino acid, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{17} is des-Xaa_{17}, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid. The C-terminus may contain a free carboxyl group or an amide group. The halo is preferably bromine, chlorine or iodine, more preferably iodine for His or Tyr and bromine for Trp. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-

phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.

More specifically, the present invention is directed to α-conotoxin peptides having the general formula III:

Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-Cys-Cys-Xaa_6-Xaa_7-Xaa_8-Xaa_9-Cys-Xaa_{10}-Xaa_{11}-Xaa_{12}-Xaa_{13}-Xaa_{14}-Xaa_{15}-Xaa_{16}-Cys-Xaa_{17}-Xaa_{18}-Xaa_{19}-Xaa_{20}-Xaa_{21}-Xaa_{22}-Xaa_{23}-Xaa_{24} (SEQ ID NO:3), wherein Xaa_1 is des-Xaa_1, Ser or Thr; Xaa_2 is des-Xaa_2, Asp, Glu, γ-carboxy-Glu (Gla), Asn, Ser or Thr; Xaa_3 is des-Xaa_3, Ala, Gly, Asn, Ser, Thr, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_4 is des-Xaa_4, Ala, Val, Leu, Ile, Gly, Glu, Gla, Gln, Asp, Asn, Phe, Pro, hydroxy-Pro or any unnatural aromatic amino acid; Xaa_5 is des-Xaa_5, Thr, Ser, Asp, Glu, Gla, Gln, Gly, Val, Asp, Asn, Ala, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_6 is Thr, Ser, Asp, Asn, Met, Val, Ala, Gly, Leu, Ile, Phe, any unnatural aromatic amino acid, Pro, hydroxy-Pro, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_7 is Ile, Leu, Val, Ser, Thr, Gln, Asn, Asp, Arg, His, halo-His, Phe, any unnatural aromatic amino acid, homoarginine, ornithine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_8 is Pro, hyroxy-Pro, Ser, Thr, Ile, Asp, Leu, Val, Gly, Ala, Phe, any unnatural aromatic amino acid, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_9 is Val, Ala, Gly, Ile, Leu, Asp, Ser, Thr, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{10} is His, halo-His, Arg, homoarginine, ornithine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Asn, Ala, Ser, Thr, Phe, Ile, Leu, Gly, Trp (D or L), neo-Trp, halo-Trp, any unnatural aromatic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{11} is Leu, Gln, Val, Ile, Gly, Met, Ala, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, Ser, Thr, Arg, homoarginine, ornithine, any unnatural basic amino acid, Asn, Glu, Gla, Gln, Phe, Trp (D or L), neo-Trp, halo-Trp or any unnatural aromatic amino acid; Xaa_{12} is Glu, Gla, Gln, Asn, Asp, Pro, hydroxy-Pro, Ser, Gly, Thr, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, Arg, homoarginine, ornithine, any unnatural basic amino acid, Phe, His, halo-

~~His, any unnatural aromatic amino acid, Leu, Met, Gly, Ala, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-~~ Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{13} is His, halo-His, Asn, Thr, Ser, Ile, Val, Leu, Phe, any unnatural aromatic amino acid, Arg, homoarginine, ornithine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Tyr, nor-Try, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{14} is Ser, Thr, Ala, Gln, Pro, hydroxy-Pro, Gly, Ile, Leu, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{15} is Asn, Glu, Gla, Asp, Gly, His, halo-His, Ala, Leu, Gln, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa_{16} is Met, Ile, Thr, Ser, Val, Leu, Pro, hydroxy-Pro, Phe, any unnatural aromatic amino acid, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, any unnatural hydroxy containing amino acid, Glu, Gla, Ala, His, halo-His, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{17} is des-Xaa_{17}, Gly, Asp, Asn, Ala, Ile, Leu, Ser, Thr, His, halo-His, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{18} is des-Xaa_{18}, Gly, Glu, Gla, Gln, Trp (D or L), neo, halo-Trp, any unnatural aromatic amino acid, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{19} is des-Xaa_{19}, Ser, Thr, Val, Ile, Ala, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{20} is des-Xaa_{20}, Val, Asp, His, halo-His, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{21} is des-Xaa_{21}, Asn, Pro or hydroxy-Pro; Xaa_{22} is des-Xaa_{22}, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa_{23} is des-Xaa_{23}, Ser or Thr; Xaa_{24} is des-Xaa_{24}, Leu, Ile or Val; with the proviso that (a) Xaa_5 is not Gly, when Xaa_1 is des-Xaa_1, Xaa_2 is des-Xaa_2, Xaa_3 is des-Xaa_3, Xaa_4 is des-Xaa_4, Xaa_6 is Ser, Xaa_7 is His, Xaa_8 is Pro, Xaa_9 is Ala, Xaa_{10} is Ser, Xaa_{11} is Val, Xaa_{12} is Asn, Xaa_{13} is Asn, Xaa_{14} is Pro, Xaa_{15} is Asp, Xaa_{16} is Ile, Xaa_{17} is des-Xaa_{17}, Xaa_{18} is des-Xaa_{18}, Xaa_{19} is des-Xaa_{19}, Xaa_{20} is des-Xaa_{20}, Xaa_{21} is des-Xaa_{21}, Xaa_{22} is des-Xaa_{22}, Xaa_{23} is des-Xaa_{23}, and Xaa_{24} is des-Xaa_{24}. The C-terminus may contain a free carboxyl group or an amide group. The halo is preferably bromine, chlorine or iodine, more preferably iodine ~~for His and Tyr and bromine for Trp. The Cys residues may be in D or L configuration and may~~

optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.

The present invention is also directed to novel specific α-conotoxin peptides of general formula I having the formulas:

Asp-Xaa$_1$-Cys-Cys-Ser-Asp-Ser-Arg-Cys-Gly-Xaa$_2$-Asn-Cys-Leu (SEQ ID NO:4);

Ala-Cys-Cys-Ser-Asp-Arg-Arg-Cys-Arg-Xaa$_3$-Arg-Cys (SEQ ID NO:5);

Phe-Thr-Cys-Cys-Arg-Arg-Gly-Thr-Cys-Ser-Gln-His-Cys (SEQ ID NO:6);

Asp-Xaa$_4$-Cys-Cys-Arg-Arg-His-Ala-Cys-Thr-Leu-Ile-Cys (SEQ ID NO:7);

Asp-Xaa$_4$-Cys-Cys-Arg-Xaa$_5$-Xaa$_5$-Cys-Thr-Leu-Ile-Cys (SEQ ID NO:8);

Gly-Cys-Cys-Ser-Asp-Xaa$_5$-Arg-Cys-Arg-Xaa$_4$-Arg-Cys-Arg (SEQ ID NO:9);

Gly-Gly-Cys-Cys-Ser-Asp-Xaa$_5$-Arg-Cys-Ala-Xaa$_3$-Arg-Cys (SEQ ID NO:10);

Ile-Ala-Xaa$_3$-Asp-Ile-Cys-Cys-Ser-Xaa$_1$-Xaa$_5$-Asp-Cys-Asn-His-Xaa$_2$-Cys-Val (SEQ ID NO:11); and

Gly-Cys-Cys-Ser-Asp-Xaa$_5$-Arg-Cys-Xaa$_2$-His-Gln-Cys (SEQ ID NO:12);

wherein Xaa$_1$ is Glu or γ-carboxy-Glu (Gla); Xaa$_2$ is Lys, N-methyl-Lys, N,N-dimethyl-Lys or N,N,N-trimethyl-Lys; Xaa$_3$ is Trp (D or L), halo-Trp or neo-Trp; Xaa$_4$ is Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr or nitro-Tyr; and Xaa$_5$ is Pro or hydroxy-Pro; and the C-terminus contains a carboxyl or amide group. The halo is preferably bromine, chlorine or iodine, more preferably iodine for Tyr and bromine for Trp. In addition, the His residues may be substituted with halo-His; the Arg residues may be substituted by Lys, ornithine, homoargine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoargine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Tyr residues may be substituted with any unnatural hydroxy containing amino acid; the Ser residues may be substituted with Thr; the Thr residues may be substituted with Ser; and the Phe and Trp residues may be substituted with any unnatural aromatic amino acid. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.

More specifically, the present invention is directed to the following α-conotoxin peptides of general formula I:

Im1.1: SEQ ID NO:4, wherein Xaa_1 is Glu and Xaa_2 is Lys;

Im1.2: SEQ ID NO:5, wherein Xaa_3 is Trp;

Rg1.2: SEQ ID NO:6;

Rg1.6: SEQ ID NO:7, wherein Xaa_4 is Tyr;

Rg1.6A: SEQ ID NO:8, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

Rg1.7: SEQ ID NO:9, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

Rg1.9: SEQ ID NO:10, wherein Xaa_3 is Trp and Xaa_5 is Pro;

Rg1.10: SEQ ID NO:11, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_3 is Trp and Xaa_5 is Pro; and

Rg1.11: SEQ ID NO:12, wherein Xaa_2 is Lys and Xaa_5 is Pro.

The C-terminus of Im1.1, Rg1.7 an Rg1.10 preferably contains a free carboxyl group. The C-terminus of Im1.2, Rg1.2, Rg1.6, Rg1.6A, Rg1.9 and Rg1.11 preferably contains an amide group.

The present invention is further directed to novel specific α-conotoxin peptides of general formula II having the formulas:

Cys-Cys-Ser-Asp-Xaa_5-Ala-Cys-Xaa_2-Gln-Thr-Xaa_5-Gly-Cys-Arg (SEQ ID NO:13);

Cys-Cys-Xaa_1-Asn-Xaa_5-Ala-Cys-Arg-His-Thr-Gln-Gly-Cys (SEQ ID NO:14);

Gly-Cys-Cys-Xaa_3-His-Xaa_5-Ala-Cys-Gly-Arg-His-Xaa_4-Cys (SEQ ID NO:15);

Ala-Xaa_5-Cys-Cys-Asn-Asn-Xaa_5-Ala-Cys-Val-Xaa_2-His-Arg-Cys (SEQ ID NO:16);

Ala-Xaa_5-Gly-Cys-Cys-Asn-Asn-Xaa_5-Ala-Cys-Val-Xaa_2-His-Arg-Cys (SEQ ID NO:17);

Xaa_5-Xaa_5-Cys-Cys-Asn-Asn-Xaa_5-Ala-Cys-Val-Xaa_2-His-Arg-Cys (SEQ ID NO:18);

Asp-Xaa_1-Asn-Cys-Cys-Xaa_3-Asn-Xaa_5-Ser-Cys-Xaa_5-Arg-Xaa_5-Arg-Cys-Thr (SEQ ID NO:19);

Gly-Cys-Cys-Ser-Thr-Xaa_5-Xaa_5-Cys-Ala-Val-Leu-Xaa_4-Cys (SEQ ID NO:20);

Gly-Cys-Cys-Gly-Asn-Xaa_5-Asp-Cys-Thr-Ser-His-Ser-Cys (SEQ ID NO:21);

Gly-Cys-Cys-Ser-Asn-Xaa_5-Xaa_5-Cys-Ala-His-Asn-Asn-Xaa_5-Asp-Cys-Arg (SEQ ID NO:42);

Gly-Cys-Cys-Xaa_4-Asn-Xaa_5-Val-Cys-Xaa_2-Xaa_2-Xaa_4-Xaa_4-Cys-Xaa_3-Xaa_2 (SEQ ID NO:154);

Xaa_6-Xaa_1-Xaa_5-Gly-Cys-Cys-Arg-His-Xaa_5-Ala-Cys-Gly-Xaa_2-Asn-Arg-Cys (SEQ ID NO:155);

Cys-Cys-Ala-Asp-Xaa_5-Asp-Cys-Arg-Phe-Arg-Xaa_5-Gly-Cys (SEQ ID NO:156);

Gly-Cys-Cys-Xaa_4-Asn-Xaa_5-Ser-Cys-Xaa_3-Xaa_5-Xaa_2-Thr-Xaa_4-Cys-Ser-Xaa_3-Xaa_2 (SEQ ID NO:157);

Cys-Cys-Ser-Asn-Xaa_5-Thr-Cys-Xaa_2-Xaa_1-Thr-Xaa_4-Gly-Cys (SEQ ID NO:158);

Cys-Cys-Ala-Asn-Xaa_5-Ile-Cys-Xaa_2-Asn-Thr-Xaa_5-Gly-Cys (SEQ ID NO:159);

Cys-Cys-Asn-Asn-Xaa_5-Thr-Cys-Xaa_2-Xaa_1-Thr-Xaa_4-Gly-Cys (SEQ ID NO:160);

Cys-Cys-Ser-Asn-Xaa_5-Val-Cys-Xaa_2-Xaa_1-Thr-Xaa_4-Gly-Cys (SEQ ID NO:161);

Gly-Gly-Cys-Cys-Ser-Xaa_4-Xaa_5-Xaa_5-Cys-Ile-Ala-Ser-Asn-Xaa_5-Xaa_2-Cys-Gly (SEQ ID NO:162);

Gly-Cys-Cys-Ser-His-Xaa_5-Val-Cys-Ser-Ala-Met-Ser-Xaa_5-Ile-Cys (SEQ ID NO:163);

Gly-Cys-Cys-Xaa_2-Asn-Xaa_5-Xaa_4-Cys-Gly-Ala-Ser-Xaa_2-Thr-Xaa_4-Cys (SEQ ID NO:164);

Gly-Cys-Cys-Ser-Xaa_4-Xaa_5-Xaa_5-Cys-Phe-Ala-Thr-Asn-Xaa_5-Asp-Cys (SEQ ID NO:165);

Gly-Gly-Cys-Cys-Ser-Xaa_4-Xaa_5-Xaa_5-Cys-Ile-Ala-Asn-Asn-Xaa_5-Leu-Cys-Ala (SEQ ID NO:166);

Gly-Gly-Cys-Cys-Ser-Xaa_4-Xaa_5-Xaa_5-Cys-Ile-Ala-Asn-Asn-Xaa_5-Phe-Cys-Ala (SEQ ID NO:167);

Asp-Cys-Cys-Ser-Asn-Xaa_5-Xaa_5-Cys-Ser-Gln-Asn-Asn-Xaa_5-Asp-Cys-Met (SEQ ID NO:168); and

~~Asp-Cys-Cys-Ser-Asn-Xaa_5-Xaa_5-Cys-Ala-His-Asn-Asn-Xaa_5-Asp-Cys-Arg (SEQ ID NO:169),~~

wherein Xaa_1 is Glu or γ-carboxy-Glu (Gla); Xaa_2 is Lys, N-methyl-Lys, N,N-dimethyl-Lys or N,N,N-trimethyl-Lys; Xaa_3 is Trp (D or L), halo-Trp or neo-Trp; Xaa_4 is Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr or nitro-Tyr; and Xaa_5 is Pro or hydroxy-Pro; and the C-terminus contains a carboxyl or amide group. The halo is preferably bromine, chlorine or iodine, more preferably iodine for Tyr and bromine for Trp. In addition, the His residues may be substituted with halo-His; the Arg residues may be substituted by Lys, ornithine, homoargine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoargine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Tyr residues may be substituted with any unnatural hydroxy containing amino acid; the Ser residues may be substituted with Thr; the Thr residues may be substituted with Ser; and the Phe and Trp residues may be substituted with any ~~unnatural aromatic amino acid. The Cys residues may be in D or L configuration and may~~

~~optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the~~ 3-hydroxyl or 2-hydroxyl isomers and ~~corresponding O-sulpho-~~ and O-phospho-derivatives. The acidic amino acid ~~residues may~~ be substituted with any synthetic acidic bioisoteric amino acid ~~surrogate, e.g., tetrazolyl derivatives of Gly and Ala.~~

More specifically, the present invention is directed to the following α-conotoxin peptides of general formula II:

Sn1.1: SEQ ID NO:13, wherein Xaa_2 is Lys and Xaa_5 is Pro;

Sn1.2: SEQ ID NO:14, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Sl1.3: SEQ ID NO:15, wherein Xaa_3 is Trp, Xaa_4 is Tyr and Xaa_5 is Pro;

A1.2: SEQ ID NO:16, wherein Xaa_2 is Lys and Xaa_5 is Pro;

Bu1.1: SEQ ID NO:17, wherein Xaa_2 is Lys and Xaa_5 is Pro;

Bu1.2: SEQ ID NO:18, wherein Xaa_2 is Lys and Xaa_5 is Pro;

Bu1.3: SEQ ID NO:19, wherein Xaa_1 is Glu, Xaa_3 is Trp and Xaa_5 is Pro;

Bu1.4: SEQ ID NO:20, wherein Xaa_4 is Tyr and Xaa_5 is Pro ;

Cr1.3: SEQ ID NO:21, wherein Xaa_5 is Pro;

Di1.1: SEQ ID NO:42 wherein Xaa_5 is Pro;

Ms1.7: SEQ ID NO:154, wherein Xaa_2 is Lys, Xaa_3 is Trp, Xaa_4 is Tyr and Xaa_5 is Pro;

P1.7: SEQ ID NO:155, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_5 is Pro and Xaa_6 is Gln;

Ms1.2: SEQ ID NO:156, wherein Xaa_5 is Pro;

Ms1.3: SEQ ID NO:157, wherein Xaa_2 is Lys, Xaa_3 is Trp, Xaa_4 is Tyr and Xaa_5 is Pro;

Ms1.4: SEQ ID NO:158, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro;

Ms1.5: SEQ ID NO:159, wherein Xaa_2 is Lys and Xaa_5 is Pro;

Ms1.8: SEQ ID NO:160, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro;

Ms1.9: SEQ ID NO:161, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro;

Bt1.7: SEQ ID NO:162, wherein Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro;

Lv1.5: SEQ ID NO:163, wherein Xaa_5 is Pro;

Ms1.10: SEQ ID NO:164, wherein Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro;

Om1.1: SEQ ID NO:165, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

R1.6: SEQ ID NO:166, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

R1.7: SEQ ID NO:167, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

Vr1.1: SEQ ID NO:168, wherein Xaa_5 is Pro; and

Vr1.2: SEQ ID NO:169, wherein Xaa_5 is Pro.

The C-terminus preferably contains a carboxyl group for the peptides Sn1.1, Sn1.2, Cr1.3, Di1.1, Ms1.2, Ms1.4, Ms1.5, Ms1.8, Ms1.9, Vr1.1 and Vr1.2. The C-terminus of the other peptides preferably contains an amide group.

The present invention is also directed to novel specific α-conotoxin peptides of general formula III having the formulas:

Gly-Cys-Cys-Ser-Asn-Xaa_5-Val-Cys-His-Leu-Xaa_1-His-Ser-Asn-Met-Cys (SEQ ID NO:22);

Gly-Cys-Cys-Ser-Asn-Xaa_5-Val-Cys-Arg-Gln-Asn-Asn-Ala-Xaa_1-Xaa_4-Cys-Arg (SEQ ID NO:23);

Xaa_5-Gln-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Xaa_1-Ile-Cys-Arg (SEQ ID NO:24);

Xaa_5-Xaa_1-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Xaa_1-Ile-Cys-Arg (SEQ ID NO:25);

Xaa_5-Gln-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Xaa_1-Ile-Cys-Asp (SEQ ID NO:26);

Xaa_5-Arg-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Xaa_1-Ile-Cys-Arg (SEQ ID NO:27);

Xaa_5-Gln-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Gly-Ile-Cys-Arg (SEQ ID NO:28);

Xaa_5-Gln-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Xaa_1-Thr-Cys-Arg (SEQ ID NO:29);

Xaa_5-Gln-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Xaa_1-Val-Cys-Arg (SEQ ID NO:30);

Xaa_5-Gln-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Ile-Asp-His-Xaa_5-Xaa_1-Ile-Cys-Arg (SEQ ID NO:31);

Xaa_5-Gln-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Xaa_1-Ile-Cys-Arg-Arg-Arg-Arg (SEQ ID NO:32);

Gly-Gly-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Ala-Val-Asn-His-Xaa_5-Xaa_1-Leu-Cys (SEQ ID NO:33);

Gly-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Ser-Val-Asn-His-Xaa_5-Xaa_1-Leu-Cys(SEQIDNO:34);

Gly-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Xaa_1-Ile-Cys (SEQ ID NO:35);

Gly-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Ser-Gly-Xaa_2-Thr-Gln-Xaa_1-Xaa_5-Cys-Arg-Xaa_1-Ser (SEQ ID NO:36);

Xaa_5-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Ser-Gly-Asn-Asn-Xaa_5-Xaa_1-Phe-Cys-Arg-Gln (SEQ ID NO:37);

Gly-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Ser-Gly-Asn-Asn-Xaa_5-Xaa_1-Phe-Cys-Arg-Gln (SEQ ID NO:38);

Gly-Cys-Cys-Ser-His-Xaa_5-Xaa_5-Cys-Ala-Met-Asn-Asn-Xaa_5-Asp-Xaa_4-Cys (SEQ ID NO:39);

Gly-Cys-Cys-Ser-His-Xaa_5-Xaa_5-Cys-Phe-Leu-Asn-Asn-Xaa_5-Asp-Xaa_4-Cys (SEQ ID NO:40);

Gly-Cys-Cys-Ser-Asn-Xaa_5-Xaa_5-Cys-Ile-Ala-Xaa_2-Asn-Xaa_5-His-Met-Cys-Gly (SEQ ID NO:41);

Gly-Cys-Cys-Ser-Asn-Xaa_5-Ala-Cys-Ala-Gly-Asn-Asn-Xaa_5-His-Val-Cys-Arg-Gln (SEQ ID NO:43);

Gly-Cys-Cys-Ser-Arg-Xaa_5-Ala-Cys-Ile-Ala-Asn-Asn-Xaa_5-Asp-Leu-Cys (SEQ ID NO:44);

Gly-Cys-Cys-Ser-Asn-Xaa_5-Val-Cys-His-Val-Xaa_1-His-Xaa_5-Xaa_1-Leu-Cys-Arg-Arg-Arg-Arg (SEQ ID NO:45);

Gly-Gly-Cys-Cys-Ser-Phe-Xaa_5-Ala-Cys-Arg-Xaa_2-Xaa_5-Arg-Xaa_5-Xaa_1-Met-Cys-Gly(SEQ ID NO:46);

Xaa_5-Xaa_1-Cys-Cys-Ser-Asp-Xaa_5-Arg-Cys-Asn-Ser-Ser-His-Xaa_5-Xaa_1-Leu-Cys-Gly(SEQ ID NO:47);

Xaa_5-Gln-Cys-Cys-Ser-Asp-Xaa_5-Arg-Cys-Asn-Val-Gly-His-Xaa_5-Xaa_1-Leu-Cys-Gly(SEQ ID NO:48);

Xaa_6-Val-Cys-Cys-Ser-Asp-Xaa_5-Arg-Cys-Asn-Val-Gly-His-Xaa_5-Xaa_1-Ile-Cys-Gly (SEQ ID NO:49);

Gly-Cys-Cys-Ser-Arg-Xaa_5-Xaa_5-Cys-Ile-Ala-Asn-Asn-Xaa_5-Asp-Leu-Cys (SEQ ID NO:50);

Xaa_5-Gln-Cys-Cys-Ser-His-Leu-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Xaa_1-Ile-Cys-Arg (SEQ ID NO:51);

Gly-Cys-Cys-Ser-Xaa_4-Phe-Asp-Cys-Arg-Met-Met-Phe-Xaa_5-Xaa_1-Met-Cys-Gly-Xaa_3-Arg (SEQ ID NO:52);

Gly-Gly-Cys-Cys-Ser-Phe-Ala-Ala-Cys-Arg-Xaa_2-Xaa_4-Arg-Xaa_5-Xaa_1-Met-Cys-Gly(SEQ ID NO:53);

Gly-Gly-Cys-Cys-Phe-His-Xaa_5-Val-Cys-Xaa_4-Ile-Asn-Leu-Leu-Xaa_1-Met-Cys-Arg-Gln-Arg (SEQ ID NO:54);

Ser-Ala-Thr-Cys-Cys-Asn-Xaa_4-Xaa_5-Xaa_5-Cys-Xaa_4-Xaa_1-Thr-Xaa_4-Xaa_5-Xaa_1-Ser-Cys-Leu (SEQ ID NO:55);

Ala-Cys-Cys-Ala-Xaa_4-Xaa_5-Xaa_5-Cys-Phe-Xaa_1-Ala-Xaa_4-Xaa_5-Xaa_1-Arg-Cys-Leu (SEQ ID NO:56);

Asn-Ala-Xaa_1-Cys-Cys-Xaa_4-Xaa_4-Xaa_5-Xaa_5-Cys-Xaa_4-Xaa_1-Ala-Xaa_4-Xaa_5-Xaa_1-Ile-Cys-Leu (SEQ ID NO:57);

Xaa_1-Cys-Cys-Thr-Asn-Xaa_5-Val-Cys-His-Ala-Xaa_1-His-Gln-Xaa_1-Leu-Cys-Ala-Arg-Arg-Arg (SEQ ID NO:170);

Gly-Cys-Cys-Ser-Asn-Xaa_5-Val-Cys-His-Leu-Xaa_1-His-Ser-Asn-Leu-Cys (SEQ ID NO:171);

Xaa_1-Cys-Cys-Thr-Asn-Xaa_5-Val-Cys-His-Val-Xaa_1-His-Gln-Xaa_1-Leu-Cys-Ala-Arg-Arg-Arg (SEQ ID NO:172);

Xaa_6-Xaa_1-Cys-Cys-Ser-Xaa_4-Xaa_5-Ala-Cys-Asn-Leu-Asp-His-Xaa_5-Xaa_1-Leu-Cys (SEQ ID NO:173);

Xaa_5-Xaa_1-Cys-Cys-Ser-Asp-Xaa_5-Arg-Cys-Asn-Ser-Thr-His-Xaa_5-Xaa_1-Leu-Cys-Gly(SEQ ID NO:174);

Leu-Asn-Cys-Cys-Met-Ile-Xaa_5-Xaa_5-Cys-Xaa_3-Xaa_2-Xaa_2-Xaa_4-Gly-Asp-Arg-Cys-Ser-Xaa_1-Val-Arg (SEQ ID NO:175);

Ala-Phe-Gly-Cys-Cys-Asp-Leu-Ile-Xaa_5-Cys-Leu-Xaa_1-Arg-Xaa_4-Gly-Asn-Arg-Cys-Asn-Xaa_1-Val-His (SEQ ID NO:176);

Leu-Gly-Cys-Cys-Asn-Val-Thr-Xaa_5-Cys-Xaa_3-Xaa_1-Xaa_2-Xaa_4-Gly-Asp-Xaa_2-Cys-Asn-Xaa_1-Val-Arg (SEQ ID NO:177);

Asp-Xaa_1-Cys-Cys-Ser-Asn-Xaa_5-Ala-Cys-Arg-Val-Asn-Asn-Xaa_5-His-Val-Cys-Arg-Arg-Arg (SEQ ID NO:178);

Leu-Asn-Cys-Cys-Ser-Ile-Xaa$_5$-Gly-Cys-Xaa$_3$-Asn-Xaa$_1$-Xaa$_4$-Xaa$_2$-Asp-Arg-Cys-Ser-Xaa$_2$-Val-Arg (SEQ ID NO:179);

Gly-Gly-Cys-Cys-Ser-His-Xaa$_5$-Val-Cys-Xaa$_4$-Phe-Asn-Asn-Xaa$_5$-Gln-Met-Cys-Arg (SEQ ID NO:180);

Gly-Gly-Cys-Cys-Ser-His-Xaa$_5$-Val-Cys-Asn-Leu-Asn-Asn-Xaa$_5$-Gln-Met-Cys-Arg (SEQ ID NO:181);

Gly-Cys-Cys-Ser-His-Xaa$_5$-Xaa$_5$-Cys-Xaa$_4$-Ala-Asn-Asn-Gln-Ala-Xaa$_4$-Cys-Asn (SEQ ID NO:182);

Gly-Gly-Cys-Cys-Ser-His-Xaa$_5$-Ala-Cys-Ser-Val-Thr-His-Xaa$_5$-Xaa$_1$-Leu-Cys (SEQ ID NO:183);

Gly-Gly-Cys-Cys-Ser-Xaa$_4$-Xaa$_5$-Ala-Cys-Ser-Val-Xaa$_1$-His-Gln-Asp-Leu-Cys-Asp (SEQ ID NO:184);

Val-Ser-Cys-Cys-Val-Val-Arg-Xaa$_5$-Cys-Xaa$_3$-Ile-Arg-Xaa$_4$-Gln-Xaa$_1$-Xaa$_1$-Cys-Leu-Xaa$_1$-Ala-Asp-Xaa$_5$-Arg-Thr-Leu (SEQ ID NO:185);

Xaa$_6$-Asn-Cys-Cys-Ser-Ile-Xaa$_5$-Gly-Cys-Xaa$_3$-Xaa$_1$-Xaa$_2$-Xaa$_4$-Gly-Asp-Xaa$_2$-Cys-Ser-Xaa$_1$-Val-Arg (SEQ ID NO:186);

Gly-Cys-Cys-Ser-Asn-Xaa$_5$-Val-Cys-His-Leu-Xaa$_1$-His-Xaa$_5$-Asn-Ala-Cys (SEQ ID NO:187);

Gly-Cys-Cys-Ser-Asn-Xaa$_5$-Ile-Cys-Xaa$_4$-Phe-Asn-Asn-Xaa$_5$-Arg-Ile-Cys-Arg (SEQ ID NO:188);

Xaa$_1$-Cys-Cys-Ser-Gln-Xaa$_5$-Xaa$_5$-Cys-Arg-Xaa$_3$-Xaa$_2$-His-Xaa$_5$-Xaa$_1$-Leu-Cys-Ser (SEQ ID NO:189);

Gly-Cys-Cys-Ser-His-Xaa$_5$-Ala-Cys-Ala-Gly-Asn-Asn-Gln-His-Ile-Cys (SEQ ID NO:190);

Gly-Cys-Cys-Ala-Val-Xaa$_5$-Ser-Cys-Arg-Leu-Arg-Asn-Xaa$_5$-Asp-Leu-Cys-Gly-Gly (SEQ ID NO:191);

Gly-Cys-Cys-Ser-His-Xaa$_5$-Ala-Cys-Asn-Val-Asn-Asn-Xaa$_5$-His-Ile-Cys(SEQIDNO:192);

Thr-Xaa$_5$-Xaa$_1$-Xaa$_1$-Cys-Cys-Xaa$_5$-Asn-Xaa$_5$-Xaa$_5$-Cys-Phe-Ala-Thr-Asn-Ser-Asp-Ile-Cys-Gly (SEQ ID NO:193);

Asp-Ala-Cys-Cys-Ser-Asp-Xaa$_5$-Arg-Cys-Ser-Gly-Xaa$_2$-His-Gln-Asp-Leu-Cys (SEQ ID NO:194);

Xaa$_1$-Asp-Cys-Cys-Ser-Asp-Xaa$_5$-Arg-Cys-Ser-Val-Gly-His-Gln-Asp-Leu-Cys (SEQ ID NO:195);

Gly-Cys-Cys-Ser-His-Xaa$_5$-Ala-Cys-Ala-Gly-Ser-Asn-Ala-His-Ile-Cys (SEQ ID NO:196);

Xaa$_1$-Asp-Cys-Cys-Ser-Asp-Xaa$_5$-Arg-Cys-Ser-Val-Gly-His-Gln-Asp-Met-Cys (SEQ ID NO:197);

Gly-Cys-Cys-Ser-His-Xaa$_5$-Ala-Cys-Ala-Gly-Asn-Asn-Xaa$_5$-His-Ile-Cys (SEQ ID NO:198);

Gly-Cys-Cys-Gly-Asn-Xaa$_5$-Ser-Cys-Ser-Ile-His-Ile-Xaa$_5$-Xaa$_4$-Val-Cys-Asn (SEQ ID NO:199);

Thr-Asp-Ser-Xaa$_1$-Xaa$_1$-Cys-Cys-Leu-Asp-Ser-Arg-Cys-Ala-Gly-Gln-His-Gln-Asp-Leu-Cys-Gly (SEQ ID NO:200);

Gly-Cys-Cys-Ser-Asn-Xaa$_5$-Xaa$_5$-Cys-Xaa$_4$-Ala-Asn-Asn-Gln-Ala-Xaa$_4$-Cys-Asn (SEQ ID NO:201);

Gly-Cys-Cys-Ser-His-Xaa$_5$-Ala-Cys-Ser-Val-Asn-Asn-Xaa$_5$-Asp-Ile-Cys (SEQ ID NO:202);

Gly-Xaa$_2$-Cys-Cys-Ile-Asn-Asp-Ala-Cys-Arg-Ser-Xaa$_2$-His-Xaa$_5$-Gln-Xaa$_4$-Cys-Ser (SEQ ID NO:203);

Gly-Cys-Cys-Xaa$_4$-Asn-Ile-Ala-Cys-Arg-Ile-Asn-Asn-Xaa$_5$-Arg-Xaa$_4$-Cys-Arg (SEQ ID NO:204);

Gly-Cys-Cys-Ser-His-Xaa$_5$-Val-Cys-Arg-Phe-Asn-Xaa$_4$-Xaa$_5$-Xaa$_2$-Xaa$_4$-Cys-Gly (SEQ ID NO:205);

Asp-Xaa$_1$-Cys-Cys-Ala-Ser-Xaa$_5$-Xaa$_5$-Cys-Arg-Leu-Asn-Asn-Xaa$_5$-Xaa$_4$-Val-Cys-His (SEQ ID NO:206);

Gly-Cys-Cys-Ser-Asn-Xaa$_5$-Val-Cys-Xaa$_3$-Gln-Asn-Asn-Ala-Xaa$_1$-Xaa$_4$-Cys-Arg-Xaa$_1$-Ser (SEQ ID NO:207);

Gly-Cys-Cys-Ser-His-Xaa$_5$-Xaa$_5$-Cys-Ala-Gln-Asn-Asn-Gln-Asp-Xaa$_4$-Cys (SEQ ID NO:208);

Gly-Cys-Cys-Ser-His-Xaa$_5$-Ala-Cys-Ser-Gly-Asn-Asn-Arg-Xaa$_1$-Xaa$_4$-Cys-Arg-Xaa$_1$-Ser (SEQ ID NO:209);

Asp-Xaa$_5$-Cys-Cys-Ser-Xaa$_4$-Xaa$_5$-Asp-Cys-Gly-Ala-Asn-His-Xaa$_5$-Xaa$_1$-Ile-Cys-Gly (SEQ ID NO:210);

Xaa$_1$-Cys-Cys-Ser-Gln-Xaa$_5$-Xaa$_5$-Cys-Arg-Xaa$_3$-Xaa$_2$-His-Xaa$_5$-Xaa$_1$-Leu-Cys-Ser (SEQ ID NO:211);

Gly-Cys-Cys-Ser-His-Xaa$_5$-Ala-Cys-Ala-Gly-Asn-Asn-Xaa$_5$-His-Ile-Cys (SEQ ID NO:212);

Gly-Cys-Cys-Ser-Asp-Xaa$_5$-Ser-Cys-Asn-Val-Asn-Asn-Xaa$_5$-Asp-Xaa$_4$-Cys (SEQ ID NO:213);

Xaa_1-Xaa_1-Cys-Cys-Ser-Asp-Xaa_5-Arg-Cys-Ser-Val-Gly-His-Gln-Asp-Met-Cys-Arg (SEQ ID NO:214);

Gly-Gly-Cys-Cys-Ser-Asn-Xaa_5-Ala-Cys-Leu-Val-Asn-His-Leu-Xaa_1-Met-Cys (SEQ ID NO:215);

Arg-Asp-Xaa_5-Cys-Cys-Phe-Asn-Xaa_5-Ala-Cys-Asn-Val-Asn-Asn-Xaa_5-Gln-Ile-Cys (SEQ ID NO:216);

Cys-Cys-Ser-Asp-Xaa_5-Ser-Cys-Xaa_3-Arg-Leu-His-Ser-Leu-Ala-Cys-Thr-Gly-Ile-Val-Asn-Arg (SEQ ID NO:217);

Cys-Cys-Thr-Asn-Xaa_5-Ala-Cys-Leu-Val-Asn-Asn-Ile-Arg-Phe-Cys-Gly(SEQIDNO:218);

Asp-Xaa_1-Cys-Cys-Ser-Asp-Xaa_5-Arg-Cys-His-Gly-Asn-Asn-Arg-Asp-His-Cys-Ala (SEQ ID NO:219);

Asp-Cys-Cys-Ser-His-Xaa_5-Leu-Cys-Arg-Leu-Phe-Val-Xaa_5-Gly-Leu-Cys-Ile (SEQ ID NO:220);

Gly-Cys-Cys-Ser-His-Xaa_5-Val-Cys-Xaa_2-Val-Arg-Xaa_4-Xaa_5-Asp-Leu-Cys-Arg (SEQ ID NO:221);

Gly-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asn-Asn-Xaa_5-His-Ile-Cys(SEQIDNO:222);

Gly-Cys-Cys-Ser-His-Xaa_5-Val-Cys-Xaa_2-Val-Arg-Xaa_4-Ser-Asp-Met-Cys (SEQ ID NO:223);

Gly-Gly-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Xaa_2-Val-His-Phe-Xaa_5-His-Ser-Cys (SEQ ID NO:224);

Val-Cys-Cys-Ser-Asn-Xaa_5-Val-Cys-His-Val-Asp-His-Xaa_5-Xaa_1-Leu-Cys-Arg-Arg-Arg-Arg (SEQ ID NO:225);

Gly-Cys-Cys-Ser-His-Xaa_5-Val-Cys-Asn-Leu-Ser-Asn-Xaa_5-Gln-Ile-Cys-Arg (SEQ ID NO:226);

Xaa_6-Xaa_1-Cys-Cys-Ser-His-Xaa_5-Ala-Cys-Asn-Val-Asp-His-Xaa_5-Xaa_1-Ile-Cys-Arg (SEQ ID NO:227);

Gly-Cys-Cys-Ser-Asn-Xaa_5-Ala-Cys-Leu-Val-Asn-His-Ile-Arg-Phe-Cys-Gly (SEQ ID NO:228);

Asp-Cys-Cys-Asp-Asp-Xaa_5-Ala-Cys-Thr-Val-Asn-Asn-Xaa_5-Gly-Leu-Cys-Thr (SEQ ID NO:229); and

~~Gly-Cys-Cys-Ser-Asn-Xaa_5-Xaa_5-Cys-Ile-Ala-Xaa_2-Asn-Xaa_5-His-Met-Cys-Gly-Gly-Arg-Arg (SEQ ID NO:230),~~

~~wherein Xaa_1 is Glu or γ-carboxy-Glu (Gla); Xaa_2 is Lys, N-methyl-Lys, N,N-dimethyl-Lys or~~ N,N,N-trimethyl-Lys; Xaa_3 is Trp (D or L), halo-Trp or neo-Trp; Xaa_4 is Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr or nitro-Tyr; and Xaa_5 is Pro or hydroxy-Pro; Xaa_6 is Gln or pyro-Glu; and the C-terminus contains a carboxyl or amide group. The halo is preferably bromine, chlorine or iodine, more preferably iodine for Tyr and bromine for Trp. In addition, the His residues may be substituted with halo-His; the Arg residues may be substituted by Lys, ornithine, homoargine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoargine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Tyr residues may be substituted with any unnatural hydroxy containing amino acid; the Ser residues may be substituted with Thr; the Thr residues may be substituted with Ser; and the Phe and Trp residues may be substituted with any unnatural aromatic amino acid. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic ~~bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.~~

More specifically, the present invention is directed to the following α-conotoxin peptides of general formula III:

SmI: SEQ ID NO:22, wherein Xaa_1 is Glu and Xaa_5 is Pro;

OB-29: SEQ ID NO:23, wherein Xaa_1 is Glu, Xaa_3 is Tyr and Xaa_5 is Pro;

Tx1.1: SEQ ID NO:24, wherein Xaa_1 is Glu and Xaa_5 is Pro;

R1.1A: SEQ ID NO:25, wherein Xaa_1 is Glu and Xaa_5 is Pro;

R1.1B: SEQ ID NO:26, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Om-9: SEQ ID NO:27, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Om-10: SEQ ID NO:28, wherein Xaa_5 is Pro;

Om-21: SEQ ID NO:29, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Om-25: SEQ ID NO:30, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Om-27: SEQ ID NO:31, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Om-28: SEQ ID NO:32, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Bt1.2: SEQ ID NO:33, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Bt1.4: SEQ ID NO:34, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Da1.1: SEQ ID NO:35, wherein Xaa_1 is Glu and Xaa_5 is Pro;

OB-20: SEQ ID NO:36, wherein Xaa_1 is Glu, Xaa_2 is Lys and Xaa_5 is Pro;

TI: SEQ ID NO:37, wherein Xaa_1 is Glu and Xaa_5 is Pro;

TIB: SEQ ID NO:38, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Pn1.1: SEQ ID NO:39, wherein Xaa_5 is Pro;

Pn1.2: SEQ ID NO:40, wherein Xaa_1 is Glu and Xaa_5 is Pro;

T1: SEQ ID NO:41, wherein Xaa_2 is Lys and Xaa_5 is Pro;

TIA: SEQ ID NO:43, wherein Xaa_5 is Pro;

Da1.2: SEQ ID NO:44, wherein Xaa_5 is Pro;

Cr1.2: SEQ ID NO:45, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Sl1.2: SEQ ID NO:46, wherein Xaa_1 is Glu, Xaa_2 is Lys and Xaa_5 is Pro;

Tx1.3: SEQ ID NO:47, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Da1.3: SEQ ID NO:48, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Da1.4: SEQ ID NO:49, wherein Xaa_1 is Glu, Xaa_5 is Pro and Xaa_6 is Gln;

Tx1.2: SEQ ID NO:50, wherein Xaa_5 is Pro;

Om-35: SEQ ID NO:51, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Sl1.1: SEQ ID NO:52, wherein Xaa_1 is Glu, Xaa_3 is Trp, Xaa_4 is Tyr and Xaa_5 is Pro;

Sl1.6: SEQ ID NO:53, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro;

Sl1.7: SEQ ID NO:54, wherein Xaa_1 is Glu Xaa_4 is Tyr and Xaa_5 is Pro;

Bt1.1: SEQ ID NO:55, wherein Xaa_1 is Glu Xaa_4 is Tyr and Xaa_5 is Pro;

Bt:1.3: SEQ ID NO:56, wherein Xaa_1 is Glu Xaa_4 is Tyr and Xaa_5 is Pro;

Bt1.5: SEQ ID NO:57, wherein Xaa_1 is Glu Xaa_4 is Tyr and Xaa_5 is Pro;

A1.4: SEQ ID NO:170, wherein Xaa_1 is Glu and Xaa_5 is Pro;

A1.5: SEQ ID NO:171, wherein Xaa_1 is Glu and Xaa_5 is Pro;

A1.6: SEQ ID NO:172, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Af1.1: SEQ ID NO:173, wherein Xaa_1 is Glu Xaa_4 is Tyr, Xaa_5 is Pro and Xaa_6 is Gln;

Af1.2: SEQ ID NO:174, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Ar1.2: SEQ ID NO:175, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_3 is Trp, Xaa_4 is Try and Xaa_5 is Pro;

Ar1.3: SEQ ID NO:176, wherein Xaa_1 is Glu, Xaa_4 is Tyr and Xaa_5 is Pro;

Ar1.4: SEQ ID NO:177, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_3 is Trp, Xaa_4 is Try and Xaa_5 is Pro;

Ar1.5: SEQ ID NO:178, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Ar1.6: SEQ ID NO:179, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_3 is Trp, Xaa_4 is Try and Xaa_5 is Pro;

Ay1.2: SEQ ID NO:180, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

Ay1.3: SEQ ID NO:181, wherein Xaa_5 is Pro;

Bn1.4: SEQ ID NO:182, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

Bt1.8: SEQ ID NO:183, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Bt1.9: SEQ ID NO:184, wherein Xaa_1 is Glu, Xaa_4 is Tyr and Xaa_5 is Pro;

Ca1.3: SEQ ID NO:185, wherein Xaa_1 is Glu, Xaa_3 is Trp, Xaa_4 is Try and Xaa_5 is Pro;

Ca1.4: SEQ ID NO:186, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_3 is Trp, Xaa_4 is Try, Xaa_5 is Pro and Xaa_6 is Gln;

C1.2: SEQ ID NO:187, wherein Xaa_1 is Glu and Xaa_5 is Pro;

C1.3: SEQ ID NO:188, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

Ep1.2: SEQ ID NO:189, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_3 is Trp and Xaa_5 is Pro;

G1.1: SEQ ID NO:190, wherein Xaa_5 is Pro;

G1.3: SEQ ID NO:191, wherein Xaa_5 is Pro;

Im1.3: SEQ ID NO:192, wherein Xaa_5 is Pro;

Lv1.2: SEQ ID NO:193, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Lv1.3: SEQ ID NO:194, wherein Xaa_2 is Lys and Xaa_5 is Pro;

Lv1.4: SEQ ID NO:195, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Lv1.6: SEQ ID NO:196, wherein Xaa_5 is Pro;

Lv1.7: SEQ ID NO:197, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Lv1.8: SEQ ID NO:198, wherein Xaa_5 is Pro;

Lv1.9: SEQ ID NO:199, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

Lv1.10: SEQ ID NO:200, wherein Xaa_1 is Glu;

Mr1.3: SEQ ID NO:201, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

Mr1.4: SEQ ID NO:202, wherein Xaa_5 is Pro;

Ms1.1: SEQ ID NO:203, wherein Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro;

Ms1.6: SEQ ID NO:204, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

O1.1: SEQ ID NO:205, wherein Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro;

O1.2: SEQ ID NO:206, wherein Xaa_1 is Glu, Xaa_4 is Tyr and Xaa_5 is Pro;

O1.4: SEQ ID NO:207, wherein Xaa_1 is Glu, Xaa_3 is Trp, Xaa_4 is Tyr and Xaa_5 is Pro;

O1.7: SEQ ID NO:208, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

O1.8: SEQ ID NO:209, wherein Xaa_1 is Glu, Xaa_4 is Tyr and Xaa_5 is Pro;

Om1.2: SEQ ID NO:210, wherein Xaa_1 is Glu, Xaa_4 is Tyr and Xaa_5 is Pro;

Om1.3: SEQ ID NO:211, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_3 is Trp and Xaa_5 is Pro;

Om1.4: SEQ ID NO:212, wherein Xaa_5 is Pro;

Om1.5: SEQ ID NO:213, wherein Xaa_4 is Tyr and Xaa_5 is Pro;

Om1.6: SEQ ID NO:214, wherein Xaa_1 is Glu and Xaa_5 is Pro;

P1.4: SEQ ID NO:215, wherein Xaa_1 is Glu and Xaa_5 is Pro;

P1.5: SEQ ID NO:216, wherein Xaa_5 is Pro;

P1.6: SEQ ID NO:217, wherein Xaa_3 is Trp and Xaa_5 is Pro;

P1.8: SEQ ID NO:218, wherein Xaa_5 is Pro;

Rg1.1: SEQ ID NO:219, wherein Xaa_1 is Glu and Xaa_5 is Pro;

Rg1.3: SEQ ID NO:220, wherein Xaa_5 is Pro;

Rg1.4: SEQ ID NO:221, wherein Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro;

Rg1.5: SEQ ID NO:222, wherein Xaa_5 is Pro;

Rg1.8: SEQ ID NO:223, wherein Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro;

Sm1.4: SEQ ID NO:224, wherein Xaa_2 is Lys and Xaa_5 is Pro;

Sm1.5: SEQ ID NO:225, wherein Xaa_1 is Glu and Xaa_5 is Pro;

S1.5: SEQ ID NO:226, wherein Xaa_5 is Pro;

Tx1.5: SEQ ID NO:227, wherein Xaa_1 is Glu, Xaa_5 is Pro and Xaa_6 is Gln;

T1.1: SEQ ID NO:228, wherein Xaa_5 is Pro;

Vr1.3: SEQ ID NO:229, wherein Xaa_5 is Pro; and

Tb: SEQ ID NO:230, wherein Xaa_2 is Lys and Xaa_5 is Pro.

The C-terminus preferably contains a carboxyl group for the peptides OB-29, Tx1.1, R1.1A, R1.1B, Om-9, Om-10, Om-21, Om-25, Om-27, Om-28, Cr1.2, Om-35, Bt1.1, Bt1.3, Bt1.5, A1.4, A1.6, Ar1.2, Ar1.3, Ar1.4, Ar1.5, Ar1.6, Ca1.3, Ca1.4, Ep1.2, Lv1.9, O1.2, Om1.3, Om1.6, P1.6, Rg1.1,

Rg1.3, Rg1.4, Sm1.5, Tx1.5 and Vr1.3. The C-terminus of the other peptides preferably contains an amide group.

~~The present invention is also directed to the novel specific α-conotoxin peptides having the~~ formulas:

Cys-Cys-Thr-Ile-Xaa_5-Ser-Cys-Xaa_4-Xaa_1-Xaa_2-Xaa_2-Xaa_2-Ile-Xaa_2-Ala-Cys-Val-Phe (SEQ ID NO:231) and

Gly-Cys-Cys-Gly-Asn-Xaa_5-Ala-Cys-Ser-Gly-Ser-Ser-Xaa_2-Asp-Ala-Xaa_5-Ser-Cys (SEQ ID NO:232),

wherein Xaa_1 is Glu or γ-carboxy-Glu (Gla); Xaa_2 is Lys, N-methyl-Lys, N,N-dimethyl-Lys or N,N,N-trimethyl-Lys; Xaa_4 is Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr or nitro-Tyr; and Xaa_5 is Pro or hydroxy-Pro; and the C-terminus contains a carboxyl or amide group. The halo is preferably bromine, chlorine or iodine, more preferably iodine for Tyr. In addition, the His residues may be substituted with halo-His; the Arg residues may be substituted by Lys, ornithine, homoargine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoargine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; the Tyr residues may be substituted with any unnatural hydroxy containing amino acid; the Ser residues may be substituted with Thr; the Thr residues may be substituted with Ser; and the Phe residues may be substituted with any unnatural aromatic amino acid. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). The Tyr residues may be substituted with the 3-hydroxyl or 2-hydroxyl isomers and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic ~~bioisoteric amino acid surrogate, e.g., tetrazolyl derivatives of Gly and Ala.~~

More specifically, the present invention is directed to the following α-conotoxin peptides:

G1.2: SEQ ID NO:231, wherein Xaa_1 is Glu, Xaa_2 is Lys, Xaa_4 is Tyr and Xaa_5 is Pro; and

Rg1.12: SEQ ID NO:232, wherein Xaa_2 is Lys and Xaa_5 is Pro.

The C-terminus of G1.2 preferably contains a carboxyl group, and the C-terminus of Rg1.12 preferably contains an amide group.

~~Examples of unnatural aromatic amino acid include, but are not limited to, such as nitro-Phe,~~ 4-substituted-Phe wherein the substituent is C_1-C_3 alkyl, ~~carboxyl,~~ hyrdroxymethyl, sulphomethyl, ~~halo, phenyl, -CHO, -CN, $-SO_3H$ and -NHAc. Examples of unnatural hydroxy containing amino~~

acid, include, but are not limited to, such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr. Examples of unnatural basic amino acids include, but are not limited to, N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolininyl]-Gly and 2-[3-(2S)pyrrolininyl]-Ala. These and other unnatural basic amino acids, unnatural hydroxy containing amino acids or unnatural aromatic amino acids are described in Building Block Index, Version 3.0 (1999 Catalog, pages 4-47 for hydroxy containing amino acids and aromatic amino acids and pages 66-87 for basic amino acids; see also http://www.amino-acids.com), incorporated herein by reference, by and available from RSP Amino Acid Analogues, Inc., Worcester, MA.

Optionally, in the peptides of general formulas I, II and III and the specific peptides described above, the Asn residues may be modified to contain an N-glycan and the Ser and Thr residues may be modified to contain an O-glycan. In accordance with the present invention, a glycan shall mean any N-, S- or O-linked mono-, di-, tri-, poly- or oligosaccharide that can be attached to any hydroxy, amino or thiol group of natural or modified amino acids by synthetic or enzymatic methodologies known in the art. The monosaccharides making up the glycan can include D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, D-talose, D-galactosamine, D-glucosamine, D-N-acetyl-glucosamine (GlcNAc), D-N-acetyl-galactosamine (GalNAc), D-fucose or D-arabinose. These saccharides may be structurally modified, e.g., with one or more O-sulfate, O-phosphate, O-acetyl or acidic groups, such as sialic acid, including combinations thereof. The gylcan may also include similar polyhydroxy groups, such as D-penicillamine 2,5 and halogenated derivatives thereof or polypropylene glycol derivatives. The glycosidic linkage is beta and 1-4 or 1-3, preferably 1-3. The linkage between the glycan and the amino acid may be alpha or beta, preferably alpha and is 1-.

Core O-glycans have been described by Van de Steen et al. (1998), incorporated herein by reference. Mucin type O-linked oligosaccharides are attached to Ser or Thr (or other hydroxylated residues of the present peptides) by a GalNAc residue. The monosaccharide building blocks and the linkage attached to this first GalNAc residue define the "core glycans," of which eight have been identified. The type of glycosidic linkage (orientation and connectivities) are defined for each core glycan. Suitable glycans and glycan analogs are described further in U.S. Serial No. 09/420,797, filed 19 October 1999 and in PCT Application No. PCT/US99/24380, filed 19 October 1999, both incorporated herein by reference. A preferred glycan is Gal(β1→3)GalNAc(α1→).

Optionally, in the peptides of general formulas I and II and the specific peptides described above, pairs of Cys residues may be replaced pairwise with Ser/(Glu or Asp) or Lys/(Glu or Asp) combinations. Sequential coupling by known methods (Barnay et al., 2000; Hruby et al., 1994; Bitan et al., 1997) allows replacement of native Cys bridges with lactam bridges.

The present invention is further directed to propeptides and nucleic acid sequences encoding the propeptides or peptides as described in further detail herein.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to relatively short peptides (termed α-conotoxins herein), about 10-30 residues in length, which are naturally available in minute amounts in the venom of the cone snails or analogous to the naturally available peptides, and which preferably include two disulfide bonds. The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of an α-conotoxin peptide. Such a pharmaceutical composition has the capability of acting as antagonists for nicotinic acetylcholine receptors. In one aspect, the α-conotoxins with specificity for neuromuscular junction nicotinic acetylcholine receptors are used as neuromuscular blocking agents for use in conjunction with surgery, as disclosed in U.S. patent application Serial No. 09/_____, filed 21 January 2000 (Attorney Docket No. 2314-178.A) and international patent application No. PCT/US00/_____, filed 21 January 2000 (Attorney Docket No. 2314-138.PCT), each incorporated by reference herein. In a second aspect, additional α-conotoxins and uses for them have been described in U.S. Patent Nos. 4,447,356 (Olivera et al., 1984); 5,432,155; 5,514,774, each incorporated herein by reference.

In a third aspect additional uses for α-conotoxins are described in U.S. Serial No. 09/219,446, filed 22 December 1998, incorporated herein by reference. In this application, α-conotoxins with specificity for neuronal nicotinic acetylcholine receptors are used for treating disorders regulated at neuronal nicotinic acetylcholine receptors. Such disorders include, but are not limited to, cardiovascular disorders, gastric motility disorders, urinary incontinence, nicotine addiction, mood disorders (such as bipolar disorder, unipolar depression, dysthymia and seasonal effective disorder) and small cell lung carcinoma, as well as the localization of small cell lung carcinoma.

The α-conotoxin peptides described herein are sufficiently small to be chemically synthesized. General chemical syntheses for preparing the foregoing α-conotoxin peptides are described hereinafter. Various ones of the α-conotoxin peptides can also be obtained by isolation

and purification from specific *Conus* species using the technique described in U.S. Patent No. 4,447,356 (Olivera et al., 1984), the disclosure of which is incorporated herein by reference.

Although the α-conotoxin peptides of the present invention can be obtained by purification from cone snails, because the amounts of α-conotoxin peptides obtainable from individual snails are very small, the desired substantially pure α-conotoxin peptides are best practically obtained in commercially valuable amounts by chemical synthesis using solid-phase strategy. For example, the yield from a single cone snail may be about 10 micrograms or less of α-conotoxin peptide. By "substantially pure" is meant that the peptide is present in the substantial absence of other biological molecules of the same type; it is preferably present in an amount of at least about 85% purity and preferably at least about 95% purity. Chemical synthesis of biologically active α-conotoxin peptides depends of course upon correct determination of the amino acid sequence.

The α-conotoxin peptides can also be produced by recombinant DNA techniques well known in the art. Such techniques are described by Sambrook et al. (1989). The peptides produced in this manner are isolated, reduced if necessary, and oxidized to form the correct disulfide bonds.

One method of forming disulfide bonds in the conantokin peptides of the present invention is the air oxidation of the linear peptides for prolonged periods under cold room temperatures or at room temperature. This procedure results in the creation of a substantial amount of the bioactive, disulfide-linked peptides. The oxidized peptides are fractionated using reverse-phase high performance liquid chromatography (HPLC) or the like, to separate peptides having different linked configurations. Thereafter, either by comparing these fractions with the elution of the native material or by using a simple assay, the particular fraction having the correct linkage for maximum biological potency is easily determined. However, because of the dilution resulting from the presence of other fractions of less biopotency, a somewhat higher dosage may be required.

The peptides are synthesized by a suitable method, such as by exclusively solid-phase techniques, by partial solid-phase techniques, by fragment condensation or by classical solution couplings.

In conventional solution phase peptide synthesis, the peptide chain can be prepared by a series of coupling reactions in which constituent amino acids are added to the growing peptide chain in the desired sequence. Use of various coupling reagents, e.g., dicyclohexylcarbodiimide or diisopropylcarbonyldimidazole, various active esters, e.g., esters of N-hydroxyphthalimide or N-hydroxy-succinimide, and the various cleavage reagents, to carry out reaction in solution, with subsequent isolation and purification of intermediates, is well known classical peptide methodology.

Classical solution synthesis is described in detail in the treatise, "Methoden der Organischen Chemie (Houben-Weyl): Synthese von Peptiden," (1974). Techniques of exclusively solid-phase synthesis are set forth in the textbook, "Solid-Phase Peptide Synthesis," (Stewart and Young, 1969), and are exemplified by the disclosure of U.S. Patent 4,105,603 (Vale et al., 1978). The fragment condensation method of synthesis is exemplified in U.S. Patent 3,972,859 (1976). Other available syntheses are exemplified by U.S. Patents No. 3,842,067 (1974) and 3,862,925 (1975). The synthesis of peptides containing γ-carboxyglutamic acid residues is exemplified by Rivier et al. (1987), Nishiuchi et al. (1993) and Zhou et al. (1996).

Common to such chemical syntheses is the protection of the labile side chain groups of the various amino acid moieties with suitable protecting groups which will prevent a chemical reaction from occurring at that site until the group is ultimately removed. Usually also common is the protection of an α-amino group on an amino acid or a fragment while that entity reacts at the carboxyl group, followed by the selective removal of the α-amino protecting group to allow subsequent reaction to take place at that location. Accordingly, it is common that, as a step in such a synthesis, an intermediate compound is produced which includes each of the amino acid residues located in its desired sequence in the peptide chain with appropriate side-chain protecting groups linked to various ones of the residues having labile side chains.

As far as the selection of a side chain amino protecting group is concerned, generally one is chosen which is not removed during deprotection of the α-amino groups during the synthesis. However, for some amino acids, e.g., His, protection is not generally necessary. In selecting a particular side chain protecting group to be used in the synthesis of the peptides, the following general rules are followed: (a) the protecting group preferably retains its protecting properties and is not split off under coupling conditions, (b) the protecting group should be stable under the reaction conditions selected for removing the α-amino protecting group at each step of the synthesis, and (c) the side chain protecting group must be removable, upon the completion of the synthesis containing the desired amino acid sequence, under reaction conditions that will not undesirably alter the peptide chain.

It should be possible to prepare many, or even all, of these peptides using recombinant DNA technology. However, when peptides are not so prepared, they are preferably prepared using the Merrifield solid-phase synthesis, although other equivalent chemical syntheses known in the art can also be used as previously mentioned. Solid-phase synthesis is commenced from the C-terminus of the peptide by coupling a protected α-amino acid to a suitable resin. Such a starting material can

be prepared by attaching an α-amino-protected amino acid by an ester linkage to a chloromethylated resin or a hydroxymethyl resin, or by an amide bond to a benzhydrylamine (BHA) resin or para-methylbenzhydrylamine (MBHA) resin. Preparation of the hydroxymethyl resin is described by Bodansky et al. (1966). Chloromethylated resins are commercially available from Bio Rad Laboratories (Richmond, CA) and from Lab. Systems, Inc. The preparation of such a resin is described by Stewart and Young (1969). BHA and MBHA resin supports are commercially available, and are generally used when the desired polypeptide being synthesized has an unsubstituted amide at the C-terminus. Thus, solid resin supports may be any of those known in the art, such as one having the formulae -O-CH_2-resin support, -NH BHA resin support, or -NH-MBHA resin support. When the unsubstituted amide is desired, use of a BHA or MBHA resin is preferred, because cleavage directly gives the amide. In case the N-methyl amide is desired, it can be generated from an N-methyl BHA resin. Should other substituted amides be desired, the teaching of U.S. Patent No. 4,569,967 (Kornreich et al., 1986) can be used, or should still other groups than the free acid be desired at the C-terminus, it may be preferable to synthesize the peptide using classical methods as set forth in the Houben-Weyl text (1974).

The C-terminal amino acid, protected by Boc or Fmoc and by a side-chain protecting group, if appropriate, can be first coupled to a chloromethylated resin according to the procedure set forth in K. Horiki et al. (1978), using KF in DMF at about 60°C for 24 hours with stirring, when a peptide having free acid at the C-terminus is to be synthesized. Following the coupling of the BOC-protected amino acid to the resin support, the α-amino protecting group is removed, as by using trifluoroacetic acid (TFA) in methylene chloride or TFA alone. The deprotection is carried out at a temperature between about 0°C and room temperature. Other standard cleaving reagents, such as HCl in dioxane, and conditions for removal of specific α-amino protecting groups may be used as described in Schroder & Lubke (1965).

After removal of the α-amino-protecting group, the remaining α-amino- and side chain-protected amino acids are coupled step-wise in the desired order to obtain the intermediate compound defined hereinbefore, or as an alternative to adding each amino acid separately in the synthesis, some of them may be coupled to one another prior to addition to the solid phase reactor. Selection of an appropriate coupling reagent is within the skill of the art. Particularly suitable as a coupling reagent is N,N'-dicyclohexylcarbodiimide (DCC, DIC, HBTU, HATU, TBTU in the presence of HoBt or HoAt).

The activating reagents used in the solid phase synthesis of the peptides are well known in the peptide art. Examples of suitable activating reagents are carbodiimides, such as N,N'-diisopropylcarbodiimide and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide. Other activating reagents and their use in peptide coupling are described by Schroder & Lubke (1965) and Kapoor (1970).

Each protected amino acid or amino acid sequence is introduced into the solid-phase reactor in about a twofold or more excess, and the coupling may be carried out in a medium of dimethylformamide (DMF):CH_2Cl_2 (1:1) or in DMF or CH_2Cl_2 alone. In cases where intermediate coupling occurs, the coupling procedure is repeated before removal of the α-amino protecting group prior to the coupling of the next amino acid. The success of the coupling reaction at each stage of the synthesis, if performed manually, is preferably monitored by the ninhydrin reaction, as described by Kaiser et al. (1970). Coupling reactions can be performed automatically, as on a Beckman 990 automatic synthesizer, using a program such as that reported in Rivier et al. (1978).

After the desired amino acid sequence has been completed, the intermediate peptide can be removed from the resin support by treatment with a reagent, such as liquid hydrogen fluoride or TFA (if using Fmoc chemistry), which not only cleaves the peptide from the resin but also cleaves all remaining side chain protecting groups and also the α-amino protecting group at the N-terminus if it was not previously removed to obtain the peptide in the form of the free acid. If Met is present in the sequence, the Boc protecting group is preferably first removed using trifluoroacetic acid (TFA)/ethanedithiol prior to cleaving the peptide from the resin with HF to eliminate potential S-alkylation. When using hydrogen fluoride or TFA for cleaving, one or more scavengers such as anisole, cresol, dimethyl sulfide and methylethyl sulfide are included in the reaction vessel.

Cyclization of the linear peptide is preferably affected, as opposed to cyclizing the peptide while a part of the peptido-resin, to create bonds between Cys residues. To effect such a disulfide cyclizing linkage, fully protected peptide can be cleaved from a hydroxymethylated resin or a chloromethylated resin support by ammonolysis, as is well known in the art, to yield the fully protected amide intermediate, which is thereafter suitably cyclized and deprotected. Alternatively, deprotection, as well as cleavage of the peptide from the above resins or a benzhydrylamine (BHA) resin or a methylbenzhydrylamine (MBHA), can take place at 0°C with hydrofluoric acid (HF) or TFA, followed by oxidation as described above.

~~The peptides are also synthesized using an automatic synthesizer. Amino acids are sequentially coupled to an MBHA Rink resin (typically 100 mg of resin) beginning at the C-~~

~~terminus using an Advanced Chemtech 357 Automatic Peptide Synthesizer. Couplings are carried~~ out using 1,3-diisopropylcarbodimide in N-methylpyrrolidinone (NMP) or by 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and diethylisopro- pylethylamine (DIEA). The FMOC protecting group is removed by treatment with a 20% solution of piperidine in dimethylformamide(DMF). Resins are subsequently washed with DMF (twice), followed by ~~methanol and NMP~~.

Pharmaceutical compositions containing a compound of the present invention or its pharmaceutically acceptable salts as the active ingredient can be prepared according to conventional pharmaceutical compounding techniques. See, for example, *Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, PA). Typically, an antagonistic amount of the active ingredient will be admixed with a pharmaceutically acceptable carrier. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral or parenteral. The compositions may further contain antioxidizing agents, stabilizing agents, preservatives and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. The active agent can be encapsulated to make it stable to passage through the gastrointestinal tract while at the same time allowing for passage across the blood brain barrier. See for example, WO 96/11698.

For parenteral administration, the compound may be dissolved in a pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic origin. The carrier may also contain other ingredients, for example, preservatives, suspending

agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid.

The active agent is preferably administered in an therapeutically effective amount. The actual amount administered, and the rate and time-course of administration, will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage, timing, etc., is within the responsibility of general practitioners or spealists, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of techniques and protocols can be found in *Remington's Parmaceutical Sciences*. Typically the conopeptides of the present invention exhibit their effect at a dosage range from about 0.001 mg/kg to about 250 mg/kg, preferably from about 0.05 mg/kg to about 100 mg/kg of the active ingredient, more preferably from a bout 0.1 mg/kg to about 75 mg/kg. A suitable dose can be administered in multiple sub-doses per day. Typically, a dose or sub-dose may contain from about 0.1 mg to about 500 mg of the active ingredient per unit dosage form. A more preferred dosage will contain from about 0.5 mg to about 100 mg of active ingredient per unit dosage form. Dosages are generally initiated at lower levels and increased until desired effects are achieved.

Alternatively, targeting therapies may be used to deliver the active agent more specifically to certain types of cell, by the use of targeting systems such as antibodies or cell specific ligands. Targeting may be desirable for a variety of reasons, e.g. if the agent is unacceptably toxic, or if it would otherwise require too high a dosage, or if it would not otherwise be able to enter the target cells.

The active agents, which are peptides, can also be administered in a cell based delivery system in which a DNA sequence encoding an active agent is introduced into cells designed for implantation in the body of the patient, especially in the spinal cord region. Suitable delivery systems are described in U.S. Patent No. 5,550,050 and published PCT Application Nos. WO 92/19195, WO 94/25503, WO 95/01203, WO 95/05452, WO 96/02286, WO 96/02646, WO 96/40871, WO 96/40959 and WO 97/12635. Suitable DNA sequences can be prepared synthetically for each active agent on the basis of the developed sequences and the known genetic code.

EXAMPLES

The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art or the techniques specifically described below were utilized.

EXAMPLE 1

Isolation of α-Conotoxins

Crude venom was extracted from venom ducts (Cruz et al., 1976), and the components were purified as previously described (Cartier et al., 1996a). The crude extract from venom ducts was purified by reverse phase liquid chromatography (RPLC) using a Vydac C_{18} semi-preparative column (10 x 250 mm) and elution with a linear gradient of acetonitrile in 0.1% TFA. Further purification of bioactive peaks was done on a Vydac C_{18} analytical column (4.6 x 220 mm) eluted with a gradient of acetonitrile in 0.1% TFA. The effluents were monitored at 220 nm. Peaks were collected, and aliquots were assayed for activity. Activity was monitored by assessing block of α3β4 nAChRs expressed in *Xenopus* oocytes.

The amino acid sequence of the purified peptides were determined by standard methods. The purified peptides were reduced and alkylated prior to sequencing by automated Edman degradation on an Applied Biosystems 477A Protein Sequencer with a 120A Analyzer (DNA/Peptide Facility, University of Utah) (Martinez et al., 1995; Shon et al., 1994).

In accordance with this method, peptides MII, AuIA, AuIB, AuIC, MAR-1, MAR-2, TI, OB-29, EpI, S1.1, Bn1.1, Bn1.2, Ca1.1, Ca1.2, Cn1.1, Cn1.2 and Sm1.3 were obtained.

EXAMPLE 2

Synthesis of Conopeptides

The synthesis of conopeptides, either the mature toxins or the precursor peptides, was separately performed using conventional protection chemistry as described by Cartier et al. (1996). Briefly, the linear chains were built on Rink amide resin by Fmoc procedures with 2-(1H-benzotriol-1-yl)-1,1,3,3,-tetramethyluronium tetrafluoroborated coupling using an ABI model 430A peptide sythesizer with amino acid derivatives purchased from Bachem (Torrence CA). Orthogonal protection was used on cysteines: Cys^3 and Cys^{16} were protected as the stable Cys(S-acetamidomethyl), while Cys^2 and Cys^8 were protected as the acid-labile Cys(S-trityl). After removal of the terminal Fmoc protecting group and cleavage of the peptides from the resins, the

released peptides were precipitated by filtering the reaction mixture into -10°C methyl t-butyl ether, which removed the protecting groups except on Cys[3] and Cys[16]. The peptides were dissolved in 0.1% TFA and 60% acetonitrile and purified by RPLC on a Vydac C_{18} preparative column (22 x 250 mm) and eluted at a flow rate of 20 mL/min with a gradient of acetonitrile in 0.1% TFA. The disulfide bridges in the three conopeptides were formed as described in Cartier et al. (1996). Briefly, the disulfide bridges between Cys[2] and Cys[8] were formed by air oxidation which was judged to be complete by analytical RPLC. The monocyclic peptides were purified by RPLC on a Vydac C_{18} prepartive column (22 x 250 mm) and eluted with a gradient of acetonitrile in 0.1% TFA. Removal of S-acetamidomethyl groups and closure of the disulfide bridge between Cys[3] and Cys[16] was carried out simultaneously be iodine oxidation. The cyclic peptides were purified by RPLC on a Vydac C_{18} prepartive column (22 x 250 mm) and eluted with a gradient of acetonitrile in 0.1% TFA.

EXAMPLE 3

Isolation of DNA Encoding α-Conotoxins

DNA coding for α-conotoxins was isolated and cloned in accordance with conventional techniques using general procedures well known in the art, such as described in Olivera et al. (1996). Alternatively, cDNA libraries was prepared from *Conus* venom duct using conventional techniques. DNA from single clones was amplified by conventional techniques using primers which correspond approximately to the M13 universal priming site and the M13 reverse universal priming site. Clones having a size of approximately 300 nucleotides were sequenced and screened for similarity in sequence to known α-conotoxins. The DNA sequences and encoded propeptide or peptide sequences are set forth in Tables 1-134.

TABLE 1

DNA Sequence (SEQ ID NO:58) and Protein Sequence (SEQ ID NO:59) of MII

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc cct tca gat cgt gca tct gat ggc agg aat gcc gca gcc aac gac
Phe Pro Ser Asp Arg Ala Ser Asp Gly Arg Asn Ala Ala Ala Asn Asp

aaa gcg tct gac gtg atc acg ctg gcc ctc aag gga tgc tgt tcc aac
Lys Ala Ser Asp Val Ile Thr Leu Ala Leu Lys Gly Cys Cys Ser Asn

cct gtc tgt cac ttg gag cat tca aac ctt tgt ggt aga aga cgc
Pro Val Cys His Leu Glu His Ser Asn Leu Cys Gly Arg Arg Arg
```

tgatgctcca ggaccctctg aaccacgacg ttcgagca

TABLE 2

DNA Sequence (SEQ ID NO:60) and Protein Sequence (SEQ ID NO:61) of AuIA

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cgt gca tct gat ggc agg aag gac gca gcg tct ggc
Phe Thr Ser Asp Arg Ala Ser Asp Gly Arg Lys Asp Ala Ala Ser Gly

ctg atc gct ctg acc atc aag gga tgc tgt tct tat cct ccc tgt ttc
Leu Ile Ala Leu Thr Ile Lys Gly Cys Cys Ser Tyr Pro Pro Cys Phe

gcg act aat tca gac tat tgt ggt tgacgacgct gatgctccag gaccctctga
Ala Thr Asn Ser Asp Tyr Cys Gly

accacgacgt
```

TABLE 3

DNA Sequence (SEQ ID NO:62) and Protein Sequence (SEQ ID NO:63) of AuIB

```
atg ttc acc gtg ttt ctg ttg gtc gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cgt gca tct gat ggc agg aag gac gca gcg tct ggc
Phe Thr Ser Asp Arg Ala Ser Asp Gly Arg Lys Asp Ala Ala Ser Gly

ctg att gct ctg acc atg aag gga tgc tgt tct tat cct ccc tgt ttc
Leu Ile Ala Leu Thr Met Lys Gly Cys Cys Ser Tyr Pro Pro Cys Phe

gcg act aat cca gac tgt ggt cga cga cgc tgatgctcca ggaccctctg
Ala Thr Asn Pro Asp Cys Gly Arg Arg Arg

aaccacgacg t
```

TABLE 4

DNA Sequence (SEQ ID NO:64) and Protein Sequence (SEQ ID NO:65) of Tx1.3

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc tct tca ggt cgt agt aca ttt cgt ggc agg aat gcc gca gcc aaa
Phe Ser Ser Gly Arg Ser Thr Phe Arg Gly Arg Asn Ala Ala Ala Lys

gcg tct ggc ctg gtc agt ctg act gac agg aga cca gaa tgc tgt agt
Ala Ser Gly Leu Val Ser Leu Thr Asp Arg Arg Pro Glu Cys Cys Ser

gat cct cgc tgt aac tcg agt cat cca gaa ctt tgt ggt gga aga cgc
Asp Pro Arg Cys Asn Ser Ser His Pro Glu Leu Cys Gly Gly Arg Arg

tgatgctcca ggaccctctg aaccacgacg t
```

TABLE 5

DNA Sequence (SEQ ID NO:66) and Protein Sequence (SEQ ID NO:67) of Tx1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc gcc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Ala Val Val Ser

ttc act tca gat cgt gca tct gat gac ggg aaa gcc gct gcg tct gac
Phe Thr Ser Asp Arg Ala Ser Asp Asp Gly Lys Ala Ala Ala Ser Asp

ctg atc act ctg acc atc aag gga tgc tgt tct cgt cct ccc tgt atc
Leu Ile Thr Leu Thr Ile Lys Gly Cys Cys Ser Arg Pro Pro Cys Ile

gcg aat aat cca gac ttg tgt ggt tgacgacgct gatgctccag aacggtctga
Ala Asn Asn Pro Asp Leu Cys Gly

accacgacgt tcgagcaatg ttcaccgtgt ttctgttggt tgtctt
```

TABLE 6

DNA Sequence (SEQ ID NO:68) and Protein Sequence (SEQ ID NO:69) of Tx1.1

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca ggt cgt agt aca ttt cgt ggc agg aat gcc gca gcc aaa
Phe Thr Ser Gly Arg Ser Thr Phe Arg Gly Arg Asn Ala Ala Ala Lys

gcg tct ggc ctg gtc agt ctg act gac agg aga cca caa tgc tgt tct
Ala Ser Gly Leu Val Ser Leu Thr Asp Arg Arg Pro Gln Cys Cys Ser

cat cct gcc tgt aac gta gat cat cca gaa att tgt cgt tgaagacgct
His Pro Ala Cys Asn Val Asp His Pro Glu Ile Cys Arg

gatgctccag gaccctctga accacgacgt
```

TABLE 7

DNA Sequence (SEQ ID NO:70) and Protein Sequence (SEQ ID NO:71) of R1.1A

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca ggt cgt cgt aca ttt cat ggc agg aat gcc gca gcc aaa
Phe Thr Ser Gly Arg Arg Thr Phe His Gly Arg Asn Ala Ala Ala Lys

gcg tct ggc ctg gtc agt ctg act gac agg aga cca gaa tgc tgt tct
Ala Ser Gly Leu Val Ser Leu Thr Asp Arg Arg Pro Glu Cys Cys Ser

cat cct gcc tgt aac gta gat cat cca gaa att tgt cgt tgaagacgct
His Pro Ala Cys Asn Val Asp His Pro Glu Ile Cys Arg

gatgctccag gaccctctga accacgacgt
```

TABLE 8

DNA Sequence (SEQ ID NO:72) and Protein Sequence (SEQ ID NO:73) of R1.1B

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser
```

```
ttc act tca ggt cgt agt aca ttt cgt ggc agg aat gcc gca gcc aaa
Phe Thr Ser Gly Arg Ser Thr Phe Arg Gly Arg Asn Ala Ala Ala Lys

gcg tct ggc ctg gtc agt ctg act gac agg aga cca caa tgc tgt tct
Ala Ser Gly Leu Val Ser Leu Thr Asp Arg Arg Pro Gln Cys Cys Ser

cat cct gcc tgt aac gta gat cat cca gaa att tgc gat tgaagacgct
His Pro Ala Cys Asn Val Asp His Pro Glu Ile Cys Asp

gatgctccag gaccctctga accacgacgt
```

TABLE 9

DNA Sequence (SEQ ID NO:74) and Protein Sequence (SEQ ID NO:75) of S1.1

```
atg ttc act gtg ttt ctg ttg gtt gtc ttg gca atc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Ile Thr Val Val Ser

ttc cct tta gat cgt gaa tct gat ggc gcg aat gcc gaa gcc cgc acc
Phe Pro Leu Asp Arg Glu Ser Asp Gly Ala Asn Ala Glu Ala Arg Thr

cac gat cat gag aag cac gca ctg gac cgg aat gga tgc tgt agg aat
His Asp His Glu Lys His Ala Leu Asp Arg Asn Gly Cys Cys Arg Asn

cct gcc tgt gag agc cac aga tgt ggt tgacgacgct gatgctccag
Pro Ala Cys Glu Ser His Arg Cys Gly

gaccctctga accacgacgt tcgagca
```

TABLE 10

DNA Sequence (SEQ ID NO:76) and Protein Sequence (SEQ ID NO:77) of Bn1.1

```
atg ttc acc atg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Met Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc gct tca gat cgt gca tct gat ggc agg aat gcc gca gcc aag gac
Phe Ala Ser Asp Arg Ala Ser Asp Gly Arg Asn Ala Ala Ala Lys Asp

aaa gcg tct gac ctg gtc gct ctg acc gtc aag gga tgc tgt tct cat
Lys Ala Ser Asp Leu Val Ala Leu Thr Val Lys Gly Cys Cys Ser His

cct gcc tgt agc gtg aat aat cca gac att tgt ggt tgaagacgct
Pro Ala Cys Ser Val Asn Asn Pro Asp Ile Cys Gly

gatgctccag gaccctctga accacgacgt tcgagca
```

TABLE 11

DNA Sequence (SEQ ID NO:78) and Protein Sequence (SEQ ID NO:79) of Bn1.2

```
aaa gaa tgc tgt act cat cct gcc tgt cac gtg agt cat cca gaa ctc
Lys Glu Cys Cys Thr His Pro Ala Cys His Val Ser His Pro Glu Leu

tgt ggt tgaaaagcga cgtgacgctc caggaccctc tgaaccacga cgttcgagca
Cys Gly
```

TABLE 12

DNA Sequence (SEQ ID NO:80) and Protein Sequence (SEQ ID NO:81) of Bn1.3

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca act gct gtt ctt cca
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Ala Val Leu Pro

gtc act tta gat cgt gca tct gat gga agg aat gca gca gcc aac gcc
Val Thr Leu Asp Arg Ala Ser Asp Gly Arg Asn Ala Ala Ala Asn Ala

aaa acg cct cgc ctg atc gcg cca ttc atc agg gat tat tgc tgt cat
Lys Thr Pro Arg Leu Ile Ala Pro Phe Ile Arg Asp Tyr Cys Cys His

aga ggt ccc tgt atg gta tgg tgt ggt tgaagccgct gctgctccag
Arg Gly Pro Cys Met Val Trp Cys Gly

gaccctctga accac
```

TABLE 13

DNA Sequence (SEQ ID NO:82) and Protein Sequence (SEQ ID NO:83) of Ca1.1

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtg gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cgt gct tct gat ggc agg aat gcc gca gcc aac gcg
Phe Thr Ser Asp Arg Ala Ser Asp Gly Arg Asn Ala Ala Ala Asn Ala

ttt gac ctg atc gct ctg atc gcc agg caa aat tgc tgt agc att ccc
Phe Asp Leu Ile Ala Leu Ile Ala Arg Gln Asn Cys Cys Ser Ile Pro

agc tgt tgg gag aaa tat aaa tgt agt taa
Ser Cys Trp Glu Lys Tyr Lys Cys Ser
```

TABLE 14

DNA Sequence (SEQ ID NO:84) and Protein Sequence (SEQ ID NO:85) of Ca1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtg gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cgt gcg tct gaa ggc agg aat gct gca gcc aag gac
Phe Thr Ser Asp Arg Ala Ser Glu Gly Arg Asn Ala Ala Ala Lys Asp

aaa gcg tct gac ctg gtg gct ctg aca gtc agg gga tgc tgt gcc att
Lys Ala Ser Asp Leu Val Ala Leu Thr Val Arg Gly Cys Cys Ala Ile

cgt gaa tgt cgc ttg cag aat gca gcg tat tgt ggt gga ata tac
Arg Glu Cys Arg Leu Gln Asn Ala Ala Tyr Cys Gly Gly Ile Tyr

tgatgctcca ggaccctctg aaccacgacg
```

TABLE 15

DNA Sequence (SEQ ID NO:86) and Protein Sequence (SEQ ID NO:87) of TIB

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser
```

```
ttc cct tca gat att gca act gag ggc agg aat gcc gca gcc aaa gcg
Phe Pro Ser Asp Ile Ala Thr Glu Gly Arg Asn Ala Ala Ala Lys Ala

ttt gac ctg ata tct tcg atc gtc aag aaa gga tgc tgt tcc cat cct
Phe Asp Leu Ile Ser Ser Ile Val Lys Lys Gly Cys Cys Ser His Pro

gcc tgt tcg ggg aat aat cca gaa ttt tgt cgt caa ggt cgc
Ala Cys Ser Gly Asn Asn Pro Glu Phe Cys Arg Gln Gly Arg

tgatgctcca ggaccctctg aaccacgacg t
```

TABLE 16

DNA Sequence (SEQ ID NO:88) and Protein Sequence (SEQ ID NO:89) of TIA

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc cct tca gat ata gca act gag ggc agg aat gcc gca gcc aaa gcg
Phe Pro Ser Asp Ile Ala Thr Glu Gly Arg Asn Ala Ala Ala Lys Ala

ttt gac ctg ata tct tcg atc gtc agg aaa gga tgc tgt tcc aat ccc
Phe Asp Leu Ile Ser Ser Ile Val Arg Lys Gly Cys Cys Ser Asn Pro

gcc tgt gcg ggg aat aat cca cat gtt tgt cgt caa ggt cgc
Ala Cys Ala Gly Asn Asn Pro His Val Cys Arg Gln Gly Arg

tgatgctcca ggaccctctg aaccacgacg t
```

TABLE 17

DNA Sequence (SEQ ID NO:90) and Protein Sequence (SEQ ID NO:91) of SI1.1

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc aat tca gat cgt gat cca gca tta ggt ggc agg aat gct gca gcc
Phe Asn Ser Asp Arg Asp Pro Ala Leu Gly Gly Arg Asn Ala Ala Ala

aaa gcg tct gac aag atc gct tcg acc ctc aag aga aga gga tgc tgt
Lys Ala Ser Asp Lys Ile Ala Ser Thr Leu Lys Arg Arg Gly Cys Cys

tcg tat ttt gac tgt aga atg atg ttt cca gaa atg tgt ggt tgg cga
Ser Tyr Phe Asp Cys Arg Met Met Phe Pro Glu Met Cys Gly Trp Arg

ggc tgatgctcca ggaccctctg aaccacgacg t
Gly
```

TABLE 18

DNA Sequence (SEQ ID NO:92) and Protein Sequence (SEQ ID NO:93) of SI1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc aat tca gat cgt gat cca gca tta ggt ggc agg aat gct gca gcc
Phe Asn Ser Asp Arg Asp Pro Ala Leu Gly Gly Arg Asn Ala Ala Ala

ata gcg tct gac aag atc gct tcg acc ctc agg aga gga gga tgc tgt
Ile Ala Ser Asp Lys Ile Ala Ser Thr Leu Arg Arg Gly Gly Cys Cys
```

```
tct ttt cct gcc tgt aga aag tat cgt cca gaa atg tgt ggt gga cga
Ser Phe Pro Ala Cys Arg Lys Tyr Arg Pro Glu Met Cys Gly Gly Arg

cgc tgatgctcca ggaccctctg aaccacgacg t
Arg
```

TABLE 19

DNA Sequence (SEQ ID NO:94) and Protein Sequence (SEQ ID NO:95) of Sl1.3

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cat gaa tct gat cgc ggt gat gcc caa acc atc caa
Phe Thr Ser Asp His Glu Ser Asp Arg Gly Asp Ala Gln Thr Ile Gln

gaa gtg ttt gag atg ttc gct ctg gac agc gat gga tgc tgt tgg cat
Glu Val Phe Glu Met Phe Ala Leu Asp Ser Asp Gly Cys Cys Trp His

cct gct tgt ggc aga cac tat tgt ggt cga aga cgc tgatgctcca
Pro Ala Cys Gly Arg His Tyr Cys Gly Arg Arg Arg

ggaccctctg aaccacgacg t
```

TABLE 20

DNA Sequence (SEQ ID NO:96) and Protein Sequence (SEQ ID NO:97) of Sl1.6

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc aat tca gat cgt gat cca gca tta ggt ggc agg aat gct gca gcc
Phe Asn Ser Asp Arg Asp Pro Ala Leu Gly Gly Arg Asn Ala Ala Ala

ata gcg tct gac aag atc gct tcg acc ctc agg aga gga gga tgc tgt
Ile Ala Ser Asp Lys Ile Ala Ser Thr Leu Arg Arg Gly Gly Cys Cys

tct ttt gct gcc tgt aga aag tat cgt cca gaa atg tgt ggt gga cga
Ser Phe Ala Ala Cys Arg Lys Tyr Arg Pro Glu Met Cys Gly Gly Arg

cgc tgatgct
Arg
```

TABLE 21

DNA Sequence (SEQ ID NO:98) and Protein Sequence (SEQ ID NO:99) of Sl1.7

```
atg ttc acc gtg ttt ctg ttg gtt ctc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Leu Leu Ala Thr Thr Val Val Ser

ttc aat tca gat cgt gca tta ggt ggc agg aat gct gca gcc aaa gcg
Phe Asn Ser Asp Arg Ala Leu Gly Gly Arg Asn Ala Ala Ala Lys Ala

tct gac aag atc ctt tcg aac ctc agg aga gga gga tgc tgt ttt cat
Ser Asp Lys Ile Leu Ser Asn Leu Arg Arg Gly Gly Cys Cys Phe His

cct gtc tgt tac atc aat ctt cta gaa atg tgt cgt caa cga ggc
Pro Val Cys Tyr Ile Asn Leu Leu Glu Met Cys Arg Gln Arg Gly

tgatcgtcca ggaccctctg aaccacgacg t
```

TABLE 22

DNA Sequence (SEQ ID NO:100) and Protein Sequence (SEQ ID NO:101) of Cn1.1

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg aca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Thr Thr Thr Val Val Ser

ttc cct tca gat agt gca tct gat gtc agg gat gac gaa gcc aaa gac
Phe Pro Ser Asp Ser Ala Ser Asp Val Arg Asp Asp Glu Ala Lys Asp

gaa agg tct gac atg tac aaa tcg aaa cgg aat gga cgc tgt tgc cat
Glu Arg Ser Asp Met Tyr Lys Ser Lys Arg Asn Gly Arg Cys Cys His

cct gcc tgt ggc aaa cac ttt agt tgt gga cgc tgatgctcca ggaccctctg
Pro Ala Cys Gly Lys His Phe Ser Cys Gly Arg

aaccacgacg t
```

TABLE 23

DNA Sequence (SEQ ID NO:102) and Protein Sequence (SEQ ID NO:103) of SmI

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

tcc cct tca gat cgt gca tct gat ggc agg aat gcc gca gcc aac gag
Ser Pro Ser Asp Arg Ala Ser Asp Gly Arg Asn Ala Ala Ala Asn Glu

aaa gcg tct gac gtg atc gcg ctg gcc ctc aag gga tgc tgt tcc aac
Lys Ala Ser Asp Val Ile Ala Leu Ala Leu Lys Gly Cys Cys Ser Asn

cct gtc tgt cac ctg gag cat tca aac atg tgt ggt aga aga cgc
Pro Val Cys His Leu Glu His Ser Asn Met Cys Gly Arg Arg Arg

tgatgctcca ggaccctctg aaccacgacg
```

TABLE 24

DNA Sequence (SEQ ID NO:104) and Protein Sequence (SEQ ID NO:105) of Bt1.1

```
atg ttc tcc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Ser Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

tcc act tca ggt ggt gca tct ggt ggc agg aag gct gca gcc aaa gcg
Ser Thr Ser Gly Gly Ala Ser Gly Gly Arg Lys Ala Ala Ala Lys Ala

tct aac cgg atc gct ctg acc gtc agg agt gca aca tgc tgt aat tat
Ser Asn Arg Ile Ala Leu Thr Val Arg Ser Ala Thr Cys Cys Asn Tyr

cct ccc tgt tac gag act tat cca gaa agt tgt ctg taacgtgaat
Pro Pro Cys Tyr Glu Thr Tyr Pro Glu Ser Cys Leu

catccagagc tttgtggctg aagacactga tgctccagga ccctctgaac cacgacgt
```

TABLE 25

DNA Sequence (SEQ ID NO:106) and Protein Sequence (SEQ ID NO:107) of Bt1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtg gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser
```

```
ttc act tca ggt cgt gca ttt cgt ggc agg aat cgc gca gcc gac gac
Phe Thr Ser Gly Arg Ala Phe Arg Gly Arg Asn Arg Ala Ala Asp Asp

aaa agg tct gac ctg gcc gct ctg agc gtc agg gga gga tgc tgt tcc
Lys Arg Ser Asp Leu Ala Ala Leu Ser Val Arg Gly Gly Cys Cys Ser

cat cct gcc tgt gcg gtg aat cat cca gag ctt tgt ggc tgaagacgct
His Pro Ala Cys Ala Val Asn His Pro Glu Leu Cys Gly

gatgccccag gaccctctga accacgacgt
```

TABLE 26

DNA Sequence (SEQ ID NO:108) and Protein Sequence (SEQ ID NO:109) of Bt1.3

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca ggt cgt gca tct ggt ggc agg aat gct gca gcc aaa gcg
Phe Thr Ser Gly Arg Ala Ser Gly Gly Arg Asn Ala Ala Ala Lys Ala

tct aac cgg atc gct atg gcc atc agc agt gga gca tgc tgt gca tat
Ser Asn Arg Ile Ala Met Ala Ile Ser Ser Gly Ala Cys Cys Ala Tyr

cct ccc tgt ttc gag gct tat cca gaa aga tgt ctg taacgtgaat
Pro Pro Cys Phe Glu Ala Tyr Pro Glu Arg Cys Leu

catccagacc tttgtggctg aagacgctga tgccccagga ccctctgaac cacgacgt
```

TABLE 27

DNA Sequence (SEQ ID NO:110) and Protein Sequence (SEQ ID NO:111) of Bt1.4

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cgt gca ttt cgt ggc agg aat tcc gca gcc aac gac
Phe Thr Ser Asp Arg Ala Phe Arg Gly Arg Asn Ser Ala Ala Asn Asp

aaa agg tct gac ctg gcc gct ctg agc gtc agg aga gga tgc tgc tcc
Lys Arg Ser Asp Leu Ala Ala Leu Ser Val Arg Arg Gly Cys Cys Ser

cat ccc gcc tgt agc gtg aat cat cca gag ctt tgt ggt aga aga cgc
His Pro Ala Cys Ser Val Asn His Pro Glu Leu Cys Gly Arg Arg Arg

tgatgcccca ggaccctctg aaccacgacg t
```

TABLE 28

DNA Sequence (SEQ ID NO:112) and Protein Sequence (SEQ ID NO:113) of Bt1.5

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca ggt cgt gca tct ggt ggc agg aat gct gca gcc aaa gcg
Phe Thr Ser Gly Arg Ala Ser Gly Gly Arg Asn Ala Ala Ala Lys Ala

tct aac cgg atc gct ctg atc gtc agg aat gca gaa tgc tgt tat tat
Ser Asn Arg Ile Ala Leu Ile Val Arg Asn Ala Glu Cys Cys Tyr Tyr
```

```
cct ccc tgt tac gag gct tat cca gaa att tgt ctg taacgtgaat
Pro Pro Cys Tyr Glu Ala Tyr Pro Glu Ile Cys Leu

catccagacc tttgtggctg aagaccctga tgctccagga ccctctgaac cacgacgt
```

TABLE 29

DNA Sequence (SEQ ID NO:114) and Protein Sequence (SEQ ID NO:115) of Pn1.1

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc att tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Ile Ser

ttc act tca gat cgt gca tct gat ggc ggg aat gcc gca gcg tct gac
Phe Thr Ser Asp Arg Ala Ser Asp Gly Gly Asn Ala Ala Ala Ser Asp

ctg atc gct ctg acc atc aag gga tgc tgt tct cat cct ccc tgt gcc
Leu Ile Ala Leu Thr Ile Lys Gly Cys Cys Ser His Pro Pro Cys Ala

atg aat aat cca gac tat tgt ggt tgacgacgct gatgctccag gaccctctga
Met Asn Asn Pro Asp Tyr Cys Gly

accacgacg
```

TABLE 30

DNA Sequence (SEQ ID NO:116) and Protein Sequence (SEQ ID NO:117) of Pn1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cgt gca tct gat ggc ggg aat gcc gca atg tct gac
Phe Thr Ser Asp Arg Ala Ser Asp Gly Gly Asn Ala Ala Met Ser Asp

ctg atc gct ctg acc atc aag gga tgc tgt tct cat cct ccc tgt ttc
Leu Ile Ala Leu Thr Ile Lys Gly Cys Cys Ser His Pro Pro Cys Phe

ctg aat aat cca gac tat tgt ggt tgacgacgct gatgctccag gaccctctga
Leu Asn Asn Pro Asp Tyr Cys Gly

accacgacg
```

TABLE 31

DNA Sequence (SEQ ID NO:118) and Protein Sequence (SEQ ID NO:119) of Sm1.3

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc cct tca gat cgt gaa tct gat ggc gcg aat gac gaa gcc cgc acc
Phe Pro Ser Asp Arg Glu Ser Asp Gly Ala Asn Asp Glu Ala Arg Thr

gac gag cct gag gag cac gga ccg gac agg aat gga tgc tgt agg aat
Asp Glu Pro Glu Glu His Gly Pro Asp Arg Asn Gly Cys Cys Arg Asn

cct gcc tgt gag agc cac aga tgt ggt tgacgacgct gatgctccag
Pro Ala Cys Glu Ser His Arg Cys Gly

gaccctctga accacgacg
```

TABLE 32

DNA Sequence (SEQ ID NO:120) and Protein Sequence (SEQ ID NO:121) of Cr1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc cct tca gat cgt gca tct gat ggc agg aat gcc gca gcc agc gac
Phe Pro Ser Asp Arg Ala Ser Asp Gly Arg Asn Ala Ala Ala Ser Asp

aga gcg tct gac gcg gcc cac cag gga tgc tgt tcc aac cct gtc tgt
Arg Ala Ser Asp Ala Ala His Gln Gly Cys Cys Ser Asn Pro Val Cys

cac gtg gaa cat cca gaa ctt tgt cgt aga aga cgc tgatgctcca
His Val Glu His Pro Glu Leu Cys Arg Arg Arg Arg

ggaccctctg aaccacgacg
```

TABLE 33

DNA Sequence (SEQ ID NO:122) and Protein Sequence (SEQ ID NO:123) of Cr1.3

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc cct tca aat cgt gaa tct gat ggc gcg aat gcc gaa gtc cgc acc
Phe Pro Ser Asn Arg Glu Ser Asp Gly Ala Asn Ala Glu Val Arg Thr

gac gag cct gag gag cac gac gaa ctg ggc ggg aat gga tgc tgt ggg
Asp Glu Pro Glu Glu His Asp Glu Leu Gly Gly Asn Gly Cys Cys Gly

aat cct gac tgt acg agc cac agt tgt gat tgacgacgct gatgctccag
Asn Pro Asp Cys Thr Ser His Ser Cys Asp

gaccctctga accacgacg
```

TABLE 34

DNA Sequence (SEQ ID NO:124) and Protein Sequence (SEQ ID NO:125) of EpI

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cgt gca tct gat agc agg aag gac gca gcg tct ggc
Phe Thr Ser Asp Arg Ala Ser Asp Ser Arg Lys Asp Ala Ala Ser Gly

ctg atc gct ctg acc atc aag gga tgc tgt tct gat cct cgc tgt aac
Leu Ile Ala Leu Thr Ile Lys Gly Cys Cys Ser Asp Pro Arg Cys Asn

atg aat aat cca gac tat tgt ggt tgacgacgct gatgctccag gaccctctga
Met Asn Asn Pro Asp Tyr Cys Gly

accacgacg
```

TABLE 35

DNA Sequence (SEQ ID NO:126) and Protein Sequence (SEQ ID NO:127) of Sn1.1

```
atg tcc acc gtg ttt ctg ttg gtt gtc ctc gca acc acc gtc gtt tcc
Met Ser Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser
```

```
ttc act gta gat cgt gca tct gat ggc agg gat gtc gca atc gac gac
Phe Thr Val Asp Arg Ala Ser Asp Gly Arg Asp Val Ala Ile Asp Asp

aga ttg gtg tct ctc cct cag atc gcc cat gct gac tgt tgt tcc gat
Arg Leu Val Ser Leu Pro Gln Ile Ala His Ala Asp Cys Cys Ser Asp

cct gcc tgc aag cag acg ccc ggt tgt cgt taaagacgct gctgctccag
Pro Ala Cys Lys Gln Thr Pro Gly Cys Arg

gaccctctga accacgacg
```

TABLE 36

DNA Sequence (SEQ ID NO:128) and Protein Sequence (SEQ ID NO:129) of Sn1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gct tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Ala Ser

ttc att atc gat gat cca tct gat ggc agg aat att gca gtc gac gac
Phe Ile Ile Asp Asp Pro Ser Asp Gly Arg Asn Ile Ala Val Asp Asp

aga ggg ctt ttc tct acg ctc ttc cat gct gat tgc tgt gaa aat cct
Arg Gly Leu Phe Ser Thr Leu Phe His Ala Asp Cys Cys Glu Asn Pro

gcc tgt aga cac acg cag ggt tgt tgatctttgt tcttcaaaga cactgctggc
Ala Cys Arg His Thr Gln Gly Cys

ccaggaccct ctgaaccacg acg
```

TABLE 37

DNA Sequence (SEQ ID NO:130) and Protein Sequence (SEQ ID NO:131) of Da1.1

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cgt gca ttt cgt ggc agg aat gcc gca gcc aaa gag
Phe Thr Ser Asp Arg Ala Phe Arg Gly Arg Asn Ala Ala Ala Lys Glu

tct ggc ctg gtc ggt ctg acc gac aag acg cga gga tgc tgt tct cat
Ser Gly Leu Val Gly Leu Thr Asp Lys Thr Arg Gly Cys Cys Ser His

cct gcc tgt aac gta gat cat cca gaa att tgt ggt tgaagacgct
Pro Ala Cys Asn Val Asp His Pro Glu Ile Cys Gly

gatgctccag gaccctctga accacgacgt
```

TABLE 38

DNA Sequence (SEQ ID NO:132) and Protein Sequence (SEQ ID NO:133) of Da1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat ggt gca tct gat gac agg aaa gcc gct gcg tct gac
Phe Thr Ser Asp Gly Ala Ser Asp Asp Arg Lys Ala Ala Ala Ser Asp

ctg atc act ctg acc atc aag gga tgc tgt tct cgt cct ccc tgt atc
Leu Ile Thr Leu Thr Ile Lys Gly Cys Cys Ser Arg Pro Pro Cys Ile
```

```
gcg aat aat cca gac ttg tgt ggt cga cga cgc tgatgctcca ggaccctctg
Ala Asn Asn Pro Asp Leu Cys Gly Arg Arg Arg
```

TABLE 39

DNA Sequence (SEQ ID NO:134) and Protein Sequence (SEQ ID NO:135) of Da1.3

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

tcc act tca ggt cgt cgt gca ttt cat ggc agg aat gcc gca gcc aaa
Ser Thr Ser Gly Arg Arg Ala Phe His Gly Arg Asn Ala Ala Ala Lys

gcg tct gga ctg gtc ggt ctg act gac agg aga cca caa tgc tgt agt
Ala Ser Gly Leu Val Gly Leu Thr Asp Arg Arg Pro Gln Cys Cys Ser

gat cct cgc tgt aac gta ggt cat cca gaa ctt tgt ggt gga aga cgc
Asp Pro Arg Cys Asn Val Gly His Pro Glu Leu Cys Gly Gly Arg Arg

tgatgctcca ggaccctctg aaccacaacg t
```

TABLE 40

DNA Sequence (SEQ ID NO:136) and Protein Sequence (SEQ ID NO:137) of Da1.4

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

tcc act tca ggt cgt gca ttt cat ggc agg aat gcc gca gcc aaa gcg
Ser Thr Ser Gly Arg Ala Phe His Gly Arg Asn Ala Ala Ala Lys Ala

tct ggc ctg gtc ggt ctg acc gac aag agg caa gta tgc tgt agt gat
Ser Gly Leu Val Gly Leu Thr Asp Lys Arg Gln Val Cys Cys Ser Asp

cct cgc tgt aac gta ggt cat cca gaa att tgt ggt gga aga cgc
Pro Arg Cys Asn Val Gly His Pro Glu Ile Cys Gly Gly Arg Arg

tgatgctcca ggaccctctg aaccacgacg t
```

TABLE 41

DNA Sequence (SEQ ID NO:138) and Protein Sequence (SEQ ID NO:139) of A1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg aca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Thr Thr Thr Val Val Ser

ttc cct tca gat agt gca tct ggt ggc agg gat gac gag gcc aaa gac
Phe Pro Ser Asp Ser Ala Ser Gly Gly Arg Asp Asp Glu Ala Lys Asp

gaa agg tct gac atg tac gaa ttg aaa cgg aat gga cgc tgt tgc cat
Glu Arg Ser Asp Met Tyr Glu Leu Lys Arg Asn Gly Arg Cys Cys His

cct gcc tgt ggt ggc aaa tac gtt aaa tgt gga cgc tgatgctcca
Pro Ala Cys Gly Gly Lys Tyr Val Lys Cys Gly Arg

ggaccctctc gaaccacg
```

TABLE 42

DNA Sequence (SEQ ID NO:140) and Protein Sequence (SEQ ID NO:141) of Bu1.1

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc tct aca gat gat gaa tct gat ggc tcg aat gaa gaa ccc agc gcc
Phe Ser Thr Asp Asp Glu Ser Asp Gly Ser Asn Glu Glu Pro Ser Ala

gac cag act gcc agg tcc tca atg aac agg gcg cct gga tgc tgt aac
Asp Gln Thr Ala Arg Ser Ser Met Asn Arg Ala Pro Gly Cys Cys Asn

aat cct gcc tgt gtg aag cac aga tgt gga tgacgctgat gctccaggac
Asn Pro Ala Cys Val Lys His Arg Cys Gly

cctctgaacc acgacgt
```

TABLE 43

DNA Sequence (SEQ ID NO:142) and Protein Sequence (SEQ ID NO:143) of Bu1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc tct aca gat gat gaa tct gat ggc tcg aat gaa gaa ccc agc gcc
Phe Ser Thr Asp Asp Glu Ser Asp Gly Ser Asn Glu Glu Pro Ser Ala

gac cag gct gcc agg tcc gca atg aac agg ccg cct gga tgc tgt aac
Asp Gln Ala Ala Arg Ser Ala Met Asn Arg Pro Pro Gly Cys Cys Asn

aat cct gcc tgt gtg aag cac aga tgt ggt gga tgacgctgat gctccaggac
Asn Pro Ala Cys Val Lys His Arg Cys Gly Gly

cctctgaacc acgacgt
```

TABLE 44

DNA Sequence (SEQ ID NO:144) and Protein Sequence (SEQ ID NO:145) of Bu1.3

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc cct tca gat cgt gac tct gat ggc gcg gat gcc gaa gcc agt gac
Phe Pro Ser Asp Arg Asp Ser Asp Gly Ala Asp Ala Glu Ala Ser Asp

gag cct gtt gag ttc gaa agg gac gag aat gga tgc tgt tgg aat cct
Glu Pro Val Glu Phe Glu Arg Asp Glu Asn Gly Cys Cys Trp Asn Pro

tcc tgt ccg agg ccc aga tgt aca gga cga cgc taatgctcca ggaccctctg
Ser Cys Pro Arg Pro Arg Cys Thr Gly Arg Arg

aaccacgacg t
```

TABLE 45

DNA Sequence (SEQ ID NO:146) and Protein Sequence (SEQ ID NO:170) of Bu1.4

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg aca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Thr Thr Thr Val Val Ser
```

```
ttc cct tca gat cgt gca tct gat ggc agg aat gcc gca gcc aac gac
Phe Pro Ser Asp Arg Ala Ser Asp Gly Arg Asn Ala Ala Ala Asn Asp

aaa gcg tct gac gtg gtc acg ctg gtc ctc aag gga tgc tgt tcc acc
Lys Ala Ser Asp Val Val Thr Leu Val Leu Lys Gly Cys Cys Ser Thr

cct ccc tgt gct gtg ctg tat tgt ggt aga aga cgc tgatgctcca
Pro Pro Cys Ala Val Leu Tyr Cys Gly Arg Arg Arg

ggaccctctg aaccacgacg t
```

TABLE 46

DNA Sequence (SEQ ID NO:148) and Protein Sequence (SEQ ID NO:149) of Di1.1

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttc gca tcc tct gtc acc tta
Met Phe Thr Val Phe Leu Leu Val Val Phe Ala Ser Ser Val Thr Leu

gat cgt gca tct tat ggc agg tat gcc tca ccc gtc gac aga gcg tct
Asp Arg Ala Ser Tyr Gly Arg Tyr Ala Ser Pro Val Asp Arg Ala Ser

gcc ctg atc gct cag gcc atc ctt cga gat tgc tgc tcc aat cct cct
Ala Leu Ile Ala Gln Ala Ile Leu Arg Asp Cys Cys Ser Asn Pro Pro

tgt gcc cat aat aat cca gac tgt cgt taaagacgct gcttgctcca
Cys Ala His Asn Asn Pro Asp Cys Arg

ggaccctctg aaccacgacg t
```

TABLE 47

DNA Sequence (SEQ ID NO:150) and Protein Sequence (SEQ ID NO:151) of T1

```
gga tgc tgt tct aat cct ccc tgt atc gcg aag aat cca cac atg tgt
Gly Cys Cys Ser Asn Pro Pro Cys Ile Ala Lys Asn Pro His Met Cys

ggt gga aga cgc tga
Gly Gly Arg Arg
```

TABLE 48

DNA Sequence (SEQ ID NO:152) and Protein Sequence (SEQ ID NO:153) of Cn1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc cct tca gat cgt gca tct gat ggc agg aat gcc gca gcc aac gac
Phe Pro Ser Asp Arg Ala Ser Asp Gly Arg Asn Ala Ala Ala Asn Asp

aaa gcg tct gac gtg atc acg ctg gcc ctc aag gga tgc tgt tcc aac
Lys Ala Ser Asp Val Ile Thr Leu Ala Leu Lys Gly Cys Cys Ser Asn

cct gtc tgt cac ttg gag cat tca aac ctt tgt ggt aga aga cgc
Pro Val Cys His Leu Glu His Ser Asn Leu Cys Gly Arg Arg Arg

tgatgctcca ggaccctctg aaccacgacg t
```

TABLE 49

DNA Sequence (SEQ ID NO:233) and Protein Sequence (SEQ ID NO:234) of Im1.1

```
tct gat gga aag agt gcc gcg gcc aaa gcc aaa ccg tct cac ctg acg
Ser Asp Gly Lys Ser Ala Ala Ala Lys Ala Lys Pro Ser His Leu Thr

gct cca ttc atc agg gac gaa tgc tgt tcc gat tct cgc tgt ggc aag
Ala Pro Phe Ile Arg Asp Glu Cys Cys Ser Asp Ser Arg Cys Gly Lys

aac tgt ctt tga
Asn Cys Leu
```

TABLE 50

DNA Sequence (SEQ ID NO:235) and Protein Sequence (SEQ ID NO:236) of Im1.2

```
ttt gat gga agg aat gcc cca gcc gac gac aaa gcg tct gac ctg atc
Phe Asp Gly Arg Asn Ala Pro Ala Asp Asp Lys Ala Ser Asp Leu Ile

gct caa atc gtc agg aga gca tgc tgt tcc gat cgt cgc tgt aga tgg
Ala Gln Ile Val Arg Arg Ala Cys Cys Ser Asp Arg Arg Cys Arg Trp

agg tgt ggt tga
Arg Cys Gly
```

TABLE 51

DNA Sequence (SEQ ID NO:237) and Protein Sequence (SEQ ID NO:238) of Rg1.2

```
tct gat gga agg aat gcc gca gcc gac gcc aga gcg tct ccc cgg atc
Ser Asp Gly Arg Asn Ala Ala Ala Asp Ala Arg Ala Ser Pro Arg Ile

gct ctt ttc ctc agg ttc aca tgc tgt agg aga ggt acc tgt tcc cag
Ala Leu Phe Leu Arg Phe Thr Cys Cys Arg Arg Gly Thr Cys Ser Gln

cac tgt ggt tgaagacact gctgctccag gaccctctga accacgacgt
His Cys Gly
```

TABLE 52

DNA Sequence (SEQ ID NO:239) and Protein Sequence (SEQ ID NO:240) of Rg1.6

```
tct aat gga agg aat gcc gca gcc gac gcc aaa gcg tct caa cgg atc
Ser Asn Gly Arg Asn Ala Ala Ala Asp Ala Lys Ala Ser Gln Arg Ile

gct cca ttc ctc agg gac tat tgc tgt agg aga cat gcc tgt acg ttg
Ala Pro Phe Leu Arg Asp Tyr Cys Cys Arg Arg His Ala Cys Thr Leu

att tgt ggt tgaagacgct gctgctccag gaccctctga accacgacgt
Ile Cys Gly
```

TABLE 53

DNA Sequence (SEQ ID NO:241) and Protein Sequence (SEQ ID NO:242) of Rg1.6A

```
tct aat gga agg aat gcc gca gcc gac gcc aaa gcg tct caa cgg atc
```

```
Ser Asn Gly Arg Asn Ala Ala Ala Asp Ala Lys Ala Ser Gln Arg Ile

gct cca ttc ctc agg gac tat tgc tgt agg aga cct ccc tgt acg ttg
Ala Pro Phe Leu Arg Asp Tyr Cys Cys Arg Arg Pro Pro Cys Thr Leu

att tgt ggt tgaagacgct gctgctccag gaccctctga accacgacgt
Ile Cys Gly
```

TABLE 54

DNA Sequence (SEQ ID NO:243) and Protein Sequence (SEQ ID NO:244) of Rg1.7

```
tct aat aaa agg aag aat gcc gca atg ctt gac atg atc gct caa cac
Ser Asn Lys Arg Lys Asn Ala Ala Met Leu Asp Met Ile Ala Gln His

gcc ata agg ggt tgc tgt tcc gat cct cgc tgt aga tat aga tgt cgt
Ala Ile Arg Gly Cys Cys Ser Asp Pro Arg Cys Arg Tyr Arg Cys Arg

tgaagacgct gctgctccag gaccctctga accacgacgt
```

TABLE 55

DNA Sequence (SEQ ID NO:245) and Protein Sequence (SEQ ID NO:246) of Rg1.9

```
ttt aat gga agg agt gcc gca gcc gac caa aat gcg cct ggc ctg atc
Phe Asn Gly Arg Ser Ala Ala Ala Asp Gln Asn Ala Pro Gly Leu Ile

gct caa gtc gtc aga gga ggg tgc tgt tcc gat ccc cgc tgc gcc tgg
Ala Gln Val Val Arg Gly Gly Cys Cys Ser Asp Pro Arg Cys Ala Trp

aga tgt ggt tgaagacgtt gctgctccag gaccctctga accacgacgt
Arg Cys Gly
```

TABLE 56

DNA Sequence (SEQ ID NO:247) and Protein Sequence (SEQ ID NO:248) of Rg1.10

```
ttt gat gga agg aat gcc gca gcc gac gcc aaa gtg att aac acg gtc
Phe Asp Gly Arg Asn Ala Ala Ala Asp Ala Lys Val Ile Asn Thr Val

gct cga atc gcc tgg gat ata tgc tgt tcc gaa cct gac tgt aac cat
Ala Arg Ile Ala Trp Asp Ile Cys Cys Ser Glu Pro Asp Cys Asn His

aaa tgt gtt tgaagacgct tctgctccag gaccctctga accacgacgt
Lys Cys Val
```

TABLE 57

DNA Sequence (SEQ ID NO:249) and Protein Sequence (SEQ ID NO:250) of Rg1.11

```
tct aat aaa agg aag aat gcc gca atg ctt gac atg atc gct caa cac
Ser Asn Lys Arg Lys Asn Ala Ala Met Leu Asp Met Ile Ala Gln His

gcc ata agg ggt tgc tgt tcc gat cct cgc tgt aaa cat cag tgt ggt
Ala Ile Arg Gly Cys Cys Ser Asp Pro Arg Cys Lys His Gln Cys Gly

tgaagacgct gctgctccag gaccctctga accacgacgt
```

TABLE 58

DNA Sequence (SEQ ID NO:251) and Protein Sequence (SEQ ID NO:252) of Ms1.7

```
atc aag aat aca gca gcc agc aac aaa gcg tct agc ctg gtg gct ctt
Ile Lys Asn Thr Ala Ala Ser Asn Lys Ala Ser Ser Leu Val Ala Leu

gtt gtc agg gga tgc tgt tac aat cct gtc tgc aag aaa tat tat tgt
Val Val Arg Gly Cys Cys Tyr Asn Pro Val Cys Lys Lys Tyr Tyr Cys

tgg aaa ggc tgatgctcca ggaccctctg aaccacgacg t
Trp Lys Gly
```

TABLE 59

DNA Sequence (SEQ ID NO:253) and Protein Sequence (SEQ ID NO:254) of P1.7

```
tct gaa ggc agg aat gct gaa gcc atc gac aac gcc tta gac cag agg
Ser Glu Gly Arg Asn Ala Glu Ala Ile Asp Asn Ala Leu Asp Gln Arg

gat cca aag cga cag gag ccg ggg tgc tgt agg cat cct gcc tgt ggg
Asp Pro Lys Arg Gln Glu Pro Gly Cys Cys Arg His Pro Ala Cys Gly

aag aac aga tgt gga aga cgc tgatgctcca ggaccctctg aaccacgacg t
Lys Asn Arg Cys Gly Arg Arg
```

TABLE 60

DNA Sequence (SEQ ID NO:255) and Protein Sequence (SEQ ID NO:256) of Ms1.2

```
tct gat ggc agg aat att gca gtc gac gac aga tgg tct ttc tat acg
Ser Asp Gly Arg Asn Ile Ala Val Asp Asp Arg Trp Ser Phe Tyr Thr

ctc ttc cat gct act tgc tgt gcc gat cct gac tgt aga ttc cgg ccc
Leu Phe His Ala Thr Cys Cys Ala Asp Pro Asp Cys Arg Phe Arg Pro

ggt tgt tgatctttgt tcttcaaaga cgctgctggc ccaggaccct ctgaaccacg
Gly Cys

acgt
```

TABLE 61

DNA Sequence (SEQ ID NO:257) and Protein Sequence (SEQ ID NO:258) of Ms1.3

```
atc aag aat act gca gcc agc aac aaa gcg cct agc ctg gtg gct att
Ile Lys Asn Thr Ala Ala Ser Asn Lys Ala Pro Ser Leu Val Ala Ile

gcc gtc agg gga tgc tgt tac aat cct tcc tgt tgg ccg aaa aca tat
Ala Val Arg Gly Cys Cys Tyr Asn Pro Ser Cys Trp Pro Lys Thr Tyr

tgt agt tggaaaggct gatgctccag gaccctctga accacgacgt
Cys Ser
```

TABLE 62

DNA Sequence (SEQ ID NO:259) and Protein Sequence (SEQ ID NO:260) of Ms1.4

```
tct gat agc agg aat gtc gca atc gag gac aga gtg tct gac ctg cac
Ser Asp Ser Arg Asn Val Ala Ile Glu Asp Arg Val Ser Asp Leu His

tct atg ttc ttc gat gtt tct tgc tgt agc aat cct acc tgt aaa gaa
Ser Met Phe Phe Asp Val Ser Cys Cys Ser Asn Pro Thr Cys Lys Glu

acg tat ggt tgt tgatcgttgg ttttgaagac gctgatgctc caggaccctc
Thr Tyr Gly Cys
```

TABLE 63

DNA Sequence (SEQ ID NO:261) and Protein Sequence (SEQ ID NO:262) of Ms1.5

```
tct gtt ggc agg aat att gca gtc gac gac aga ggg att ttc tct acg
Ser Val Gly Arg Asn Ile Ala Val Asp Asp Arg Gly Ile Phe Ser Thr

ctc ttc cat gct cat tgc tgt gcc aat ccc atc tgt aaa aac acg ccc
Leu Phe His Ala His Cys Cys Ala Asn Pro Ile Cys Lys Asn Thr Pro

ggt tgt tgatctttgt tcttcaaaga cgctgctggc ccaggaccct ctgaaccacg
Gly Cys

acgt
```

TABLE 64

DNA Sequence (SEQ ID NO:263) and Protein Sequence (SEQ ID NO:264) of Ms1.8

```
tcc gat ggc agg aat gtc gca atc gac gac aga gtg tct gac ctg cac
Ser Asp Gly Arg Asn Val Ala Ile Asp Asp Arg Val Ser Asp Leu His

tct atg ttc ttc gat att gct tgc tgt aac aat cct acc tgt aaa gaa
Ser Met Phe Phe Asp Ile Ala Cys Cys Asn Asn Pro Thr Cys Lys Glu

acg tat ggt tgt tgatcgttgg ttttgaagac gctgatgctc caggaccctc
Thr Tyr Gly Cys

tgaaccacga cgt
```

TABLE 65

DNA Sequence (SEQ ID NO:265) and Protein Sequence (SEQ ID NO:266) of Ms1.9

```
tct gat ggc agg aat gtc gca atc gag gac aga gtg tct gac ctg ctc
Ser Asp Gly Arg Asn Val Ala Ile Glu Asp Arg Val Ser Asp Leu Leu

tct atg ctc ttc gat gtt gct tgc tgt agc aat cct gtc tgt aaa gaa
Ser Met Leu Phe Asp Val Ala Cys Cys Ser Asn Pro Val Cys Lys Glu

acg tat ggt tgt tgatcgttgg ttttgaagac gctgatgctc caggaccctc
Thr Tyr Gly Cys

tgaaccacga cgt
```

TABLE 66

DNA Sequence (SEQ ID NO:267) and Protein Sequence (SEQ ID NO:268) of Bt1.7

```
tat gat ggc agg aat gct gcc gcc gac gac aaa gct ttt gac ctg ctg
Tyr Asp Gly Arg Asn Ala Ala Ala Asp Asp Lys Ala Phe Asp Leu Leu

gct atg acc ata agg gga gga tgc tgt tcc tat cct ccc tgt atc gcg
Ala Met Thr Ile Arg Gly Gly Cys Cys Ser Tyr Pro Pro Cys Ile Ala

agt aat cct aaa tgt ggt gga aga cgc tgatgctcca ggaccctctg
Ser Asn Pro Lys Cys Gly Gly Arg Arg

aaccacaacg t
```

TABLE 67

DNA Sequence (SEQ ID NO:269) and Protein Sequence (SEQ ID NO:270) of Lv1.5

```
ttt gat ggc agg aat gct gca ggc aac gcc aaa atg tcc gcc ctg atg
Phe Asp Gly Arg Asn Ala Ala Gly Asn Ala Lys Met Ser Ala Leu Met

gcc ctg acc atc agg gga tgc tgt tcc cat cct gtc tgt agc gcg atg
Ala Leu Thr Ile Arg Gly Cys Cys Ser His Pro Val Cys Ser Ala Met

agt cca atc tgt ggc tgaagacgct gatgccccag gaccctctga accacgacgt
Ser Pro Ile Cys Gly
```

TABLE 68

DNA Sequence (SEQ ID NO:271) and Protein Sequence (SEQ ID NO:272) of Ms1.10

```
atc aag aat gct gca gct gac gac aaa gca tct gac ctg ctc tct cag
Ile Lys Asn Ala Ala Ala Asp Asp Lys Ala Ser Asp Leu Leu Ser Gln

atc gtc agg aat gct gca tcc aat gac aaa ggg tct gac ctg atg act
Ile Val Arg Asn Ala Ala Ser Asn Asp Lys Gly Ser Asp Leu Met Thr

ctt gcc ctc agg gga tgc tgt aaa aat cct tac tgt ggt gcg tcg aaa
Leu Ala Leu Arg Gly Cys Cys Lys Asn Pro Tyr Cys Gly Ala Ser Lys

aca tat tgt ggt aga aga cgc tgatgctcca ggaccctctg aaccacgacg t
Thr Tyr Cys Gly Arg Arg Arg
```

TABLE 69

DNA Sequence (SEQ ID NO:273) and Protein Sequence (SEQ ID NO:274) of Om1.1

```
tctgatggca ggaatgccgc agcgtctgac ctgatggat ctg acc atc aag gga
                                          Leu Thr Ile Lys Gly

tgc tgt tct tat cct ccc tgt ttc gcg act aat cca gac tgt ggt cga
Cys Cys Ser Tyr Pro Pro Cys Phe Ala Thr Asn Pro Asp Cys Gly Arg

cga cgc tgatgctcca ggaccctctg aaccacgacg t
Arg Arg
```

TABLE 70

DNA Sequence (SEQ ID NO:275) and Protein Sequence (SEQ ID NO:276) of R1.6

```
ttt gat ggc agg aat gcc gca gcc gac tac aaa ggg tct gaa ttg ctc
Phe Asp Gly Arg Asn Ala Ala Ala Asp Tyr Lys Gly Ser Glu Leu Leu

gct atg acc gtc agg gga gga tgc tgt tcc tat cct ccc tgt atc gca
Ala Met Thr Val Arg Gly Gly Cys Cys Ser Tyr Pro Pro Cys Ile Ala

aat aat cct ctt tgt gct gga aga cgc tga
Asn Asn Pro Leu Cys Ala Gly Arg Arg
```

TABLE 71

DNA Sequence (SEQ ID NO:277) and Protein Sequence (SEQ ID NO:278) of R1.7

```
ttt gat ggc agg aat gcc gca gcc gac tac aaa ggg tct gaa ttg ctc
Phe Asp Gly Arg Asn Ala Ala Ala Asp Tyr Lys Gly Ser Glu Leu Leu

gct atg acc gtc agg gga gga tgc tgt tcc tat cct ccc tgt atc gca
Ala Met Thr Val Arg Gly Gly Cys Cys Ser Tyr Pro Pro Cys Ile Ala

aat aat cct ttt tgt gct gga aga cgc tga
Asn Asn Pro Phe Cys Ala Gly Arg Arg
```

TABLE 72

DNA Sequence (SEQ ID NO:279) and Protein Sequence (SEQ ID NO:280) of Vr1.1

```
tct tat gac agg tat gcc tcg ccc gtc gac aga gcg tct gcc ctg atc
Ser Tyr Asp Arg Tyr Ala Ser Pro Val Asp Arg Ala Ser Ala Leu Ile

gct cag gcc atc ctt cga gat tgc tgt tcc aat cct ccc tgt tcc caa
Ala Gln Ala Ile Leu Arg Asp Cys Cys Ser Asn Pro Pro Cys Ser Gln

aat aat cca gac tgt atg taaagacgct gcttgctcca ggaccctctg
Asn Asn Pro Asp Cys Met

aaccacgacg t
```

TABLE 73

DNA Sequence (SEQ ID NO:281) and Protein Sequence (SEQ ID NO:282) of Vr1.2

```
tct tat ggc agg tat gcc tca ccc gtc gac aga gcg tct gcc ctg atc
Ser Tyr Gly Arg Tyr Ala Ser Pro Val Asp Arg Ala Ser Ala Leu Ile

gct cag gcc atc ctt cga gat tgc tgc tcc aat cct cct tgt gcc cat
Ala Gln Ala Ile Leu Arg Asp Cys Cys Ser Asn Pro Pro Cys Ala His

aat aat cca gac tgt cgt taaagacgct gcttgctcca ggaccctctg
Asn Asn Pro Asp Cys Arg

aaccacgacg t
```

TABLE 74

DNA Sequence (SEQ ID NO:283) and Protein Sequence (SEQ ID NO:284) of A1.4

```
tct gat ggc agg aat gcc gca gcc aac gac aaa gcg tct ggc atg agc
Ser Asp Gly Arg Asn Ala Ala Ala Asn Asp Lys Ala Ser Gly Met Ser

gcg ctg gcc gtc aat gaa tgc tgt acc aac cct gtc tgt cac gcg gaa
Ala Leu Ala Val Asn Glu Cys Cys Thr Asn Pro Val Cys His Ala Glu

cat caa gaa ctt tgt gct aga aga cgc tga
His Gln Glu Leu Cys Ala Arg Arg Arg
```

TABLE 75

DNA Sequence (SEQ ID NO:285) and Protein Sequence (SEQ ID NO:286) of A1.5

```
tct gat ggc agg aat gcc gca gcc aac gac aaa gcg tct gac gtg atc
Ser Asp Gly Arg Asn Ala Ala Ala Asn Asp Lys Ala Ser Asp Val Ile

acg ctg gcc ctc aag gga tgc tgt tcc aac cct gtc tgt cac ttg gag
Thr Leu Ala Leu Lys Gly Cys Cys Ser Asn Pro Val Cys His Leu Glu

cat tca aac ctt tgt ggt aga aga cgc tga
His Ser Asn Leu Cys Gly Arg Arg Arg
```

TABLE 76

DNA Sequence (SEQ ID NO:287) and Protein Sequence (SEQ ID NO:288) of A1.6

```
tct gat ggc agg aat gcc gca gcc aac gac aaa gcg tct ggc atg agc
Ser Asp Gly Arg Asn Ala Ala Ala Asn Asp Lys Ala Ser Gly Met Ser

gcg ctg gcc gtc aat gaa tgc tgt acc aac cct gtc tgt cac gtg gaa
Ala Leu Ala Val Asn Glu Cys Cys Thr Asn Pro Val Cys His Val Glu

cat caa gaa ctt tgt gct aga aga cgc tga
His Gln Glu Leu Cys Ala Arg Arg Arg
```

TABLE 77

DNA Sequence (SEQ ID NO:289) and Protein Sequence (SEQ ID NO:290) of Af1.1

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cgt gca ttt cgt ggc agg aat gcc gca gcc aaa gcg
Phe Thr Ser Asp Arg Ala Phe Arg Gly Arg Asn Ala Ala Ala Lys Ala

tct ggc ctg gtc ggt ctg acc gac aag agg caa gaa tgc tgt tct tat
Ser Gly Leu Val Gly Leu Thr Asp Lys Arg Gln Glu Cys Cys Ser Tyr

cct gcc tgt aac cta gat cat cca gaa ctt tgt ggt tgaagacgct
Pro Ala Cys Asn Leu Asp His Pro Glu Leu Cys Gly

gatgctccag gaccctctga accacgacgt
```

TABLE 78

DNA Sequence (SEQ ID NO:291) and Protein Sequence (SEQ ID NO:292) of Af1.2

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc act gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

tcc act tca ggt cgt cgt gca ttt cgt ggc agg aat gcc gca gcc aaa
Ser Thr Ser Gly Arg Arg Ala Phe Arg Gly Arg Asn Ala Ala Ala Lys

gcg tct gga ctg gtc ggt ctg act gac agg aga cca gaa tgc tgt agt
Ala Ser Gly Leu Val Gly Leu Thr Asp Arg Arg Pro Glu Cys Cys Ser

gat cct cgc tgt aac tcg act cat cca gaa ctt tgt ggt gga aga cgc
Asp Pro Arg Cys Asn Ser Thr His Pro Glu Leu Cys Gly Gly Arg Arg

tgatgctcca ggaccctctg aaccacgacg t
```

TABLE 79

DNA Sequence (SEQ ID NO:293) and Protein Sequence (SEQ ID NO:294) of Ar1.2

```
tct gat ggc agg aat gcc gca gcc aac gcg ttt gac ctg atc gat ctg
Ser Asp Gly Arg Asn Ala Ala Ala Asn Ala Phe Asp Leu Ile Asp Leu

acc gcc agg cta aat tgc tgt atg att ccc ccc tgt tgg aag aaa tat
Thr Ala Arg Leu Asn Cys Cys Met Ile Pro Pro Cys Trp Lys Lys Tyr

gga gac aga tgt agt gaa gta cgc tgatgctcca ggaccctctg aaccacgacg
Gly Asp Arg Cys Ser Glu Val Arg

t
```

TABLE 80

DNA Sequence (SEQ ID NO:295) and Protein Sequence (SEQ ID NO:296) of Ar1.3

```
tct gat ggc agg aat gcc gca cgc aaa gcg ttt ggc tgc tgc gac tta
Ser Asp Gly Arg Asn Ala Ala Arg Lys Ala Phe Gly Cys Cys Asp Leu

ata ccc tgt ttg gag aga tat ggt aac aga tgt aat gaa gtg cac
Ile Pro Cys Leu Glu Arg Tyr Gly Asn Arg Cys Asn Glu Val His

tgatgctcca ggaccctctg aaccacgcga cgt
```

TABLE 81

DNA Sequence (SEQ ID NO:297) and Protein Sequence (SEQ ID NO:298) of Ar1.4

```
tct gat ggc agc aat gcc gca gcc aac gag ttt gac ctg atc gct ctg
Ser Asp Gly Ser Asn Ala Ala Ala Asn Glu Phe Asp Leu Ile Ala Leu

acc gcc agg cta ggt tgc tgt aac gtt aca ccc tgt tgg gag aaa tat
Thr Ala Arg Leu Gly Cys Cys Asn Val Thr Pro Cys Trp Glu Lys Tyr

gga gac aaa tgt aat gaa gta cgc tgatgcttca ggaccctctg aaccacgacg
Gly Asp Lys Cys Asn Glu Val Arg

t
```

TABLE 82

DNA Sequence (SEQ ID NO:299) and Protein Sequence (SEQ ID NO:300) of Ar1.5

```
tct gat ggc agg aat gtc gca gca aaa gcg ttt cac cgg atc ggc cgg
Ser Asp Gly Arg Asn Val Ala Ala Lys Ala Phe His Arg Ile Gly Arg

acc atc agg gat gaa tgc tgt tcc aat cct gcc tgt agg gtg aat aat
Thr Ile Arg Asp Glu Cys Cys Ser Asn Pro Ala Cys Arg Val Asn Asn

cca cac gtt tgt aga cga cgc tgatgctcca ggaccctctg aaccacgacg t
Pro His Val Cys Arg Arg Arg
```

TABLE 83

DNA Sequence (SEQ ID NO:301) and Protein Sequence (SEQ ID NO:302) of Ar1.6

```
tct gat ggc agg aat gcc gca gcc aac gcg ttt gac ctg atg cct ctg
Ser Asp Gly Arg Asn Ala Ala Ala Asn Ala Phe Asp Leu Met Pro Leu

acc gcc agg cta aat tgc tgt agc att ccc ggc tgt tgg aac gaa tat
Thr Ala Arg Leu Asn Cys Cys Ser Ile Pro Gly Cys Trp Asn Glu Tyr

aaa gac aga tgt agt aaa gta cgc tgatgctcca ggaccctctg aaccacgacg
Lys Asp Arg Cys Ser Lys Val Arg

t
```

TABLE 84

DNA Sequence (SEQ ID NO:303) and Protein Sequence (SEQ ID NO:304) of Ay1.2

```
tctgatggca ggaatgccgc agccgacgac aaagcgtctg acctggtcgc t ctg gtc
                                                        Leu Val

gtc agg gga gga tgc tgt tcc cac cct gtc tgt tac ttt aat aat cca
Val Arg Gly Gly Cys Cys Ser His Pro Val Cys Tyr Phe Asn Asn Pro

caa atg tgt cgt gga aga cgc tgatgctcca ggaccctctg aaccacgacg t
Gln Met Cys Arg Gly Arg Arg
```

TABLE 85

DNA Sequence (SEQ ID NO:305) and Protein Sequence (SEQ ID NO:306) of Ay1.3

```
tctgatggca ggaatgccgc agccgacgac aaagcgtctg acctggtcgc t ctg gcc
                                                        Leu Ala

gtc agg gga gga tgc tgt tcc cac cct gtc tgt aac ttg aat aat cca
Val Arg Gly Gly Cys Cys Ser His Pro Val Cys Asn Leu Asn Asn Pro

caa atg tgt cgt gga aga cgc tgatgctcca ggaccctctg aaccacgacg t
Gln Met Cys Arg Gly Arg Arg
```

TABLE 86

DNA Sequence (SEQ ID NO:307) and Protein Sequence (SEQ ID NO:308) of Bt1.8

```
ttt cgt ggc agg aat ccc gca gcc aac gac aaa agg tct gac ctg gcc
Phe Arg Gly Arg Asn Pro Ala Ala Asn Asp Lys Arg Ser Asp Leu Ala

gct ctg agc gtc agg gga gga tgc tgt tcc cat cct gcc tgt agc gtg
Ala Leu Ser Val Arg Gly Gly Cys Cys Ser His Pro Ala Cys Ser Val

act cat cca gag ctt tgt ggc tgaagacgct gatgccccag gaccctctga
Thr His Pro Glu Leu Cys Gly

accacgacgt
```

TABLE 87

DNA Sequence (SEQ ID NO:309) and Protein Sequence (SEQ ID NO:310) of Bt1.9

```
tct gat ggc ggg aat gcc gca gcc aaa gcg tct gac ctg atc gct cag
Ser Asp Gly Gly Asn Ala Ala Ala Lys Ala Ser Asp Leu Ile Ala Gln

acc atc agg gga gga tgc tgt tcc tat cct gcc tgt agc gtg gaa cat
Thr Ile Arg Gly Gly Cys Cys Ser Tyr Pro Ala Cys Ser Val Glu His

caa gac ctt tgt gat gga aga cgc tgatgctcca ggaccctctg aaccacgacg
Gln Asp Leu Cys Asp Gly Arg Arg

t
```

TABLE 88

DNA Sequence (SEQ ID NO:311) and Protein Sequence (SEQ ID NO:312) of Ca1.3

```
tct tat ggc agg aat gcc gca gcc aaa gcg ttt gaa gtg agt tgc tgt
Ser Tyr Gly Arg Asn Ala Ala Ala Lys Ala Phe Glu Val Ser Cys Cys

gtc gtt cgc ccc tgt tgg att cgc tat caa gag gaa tgt ctt gaa gca
Val Val Arg Pro Cys Trp Ile Arg Tyr Gln Glu Glu Cys Leu Glu Ala

gat ccc agg acc ctc tga
Asp Pro Arg Thr Leu
```

TABLE 89

DNA Sequence (SEQ ID NO:313) and Protein Sequence (SEQ ID NO:314) of Ca1.4

```
tct gat ggc agg aat gcc gca gcc aac gcc ctt gac ctg atc act ctg
Ser Asp Gly Arg Asn Ala Ala Ala Asn Ala Leu Asp Leu Ile Thr Leu

atc gcc agg caa aat tgc tgt agc att ccc ggc tgt tgg gag aaa tat
Ile Ala Arg Gln Asn Cys Cys Ser Ile Pro Gly Cys Trp Glu Lys Tyr

gga gac aaa tgt agt gaa gta cgc tga
Gly Asp Lys Cys Ser Glu Val Arg
```

TABLE 90

DNA Sequence (SEQ ID NO:315) and Protein Sequence (SEQ ID NO:316) of C1.2

```
tct gat ggc agg aat gaa gca gcc aac gac gaa gcg tct gac gtg atc
Ser Asp Gly Arg Asn Glu Ala Ala Asn Asp Glu Ala Ser Asp Val Ile
```

```
gag ctg gcc ctc aag gga tgc tgt tcc aac cct gtc tgt cac ttg gag
Glu Leu Ala Leu Lys Gly Cys Cys Ser Asn Pro Val Cys His Leu Glu

cat cca aac gct tgt ggt aga aga cgc tgatgctcca ggaccctctg
His Pro Asn Ala Cys Gly Arg Arg Arg

aaccacgacg t
```

TABLE 91

DNA Sequence (SEQ ID NO:317) and Protein Sequence (SEQ ID NO:318) of C1.3

```
tct gat ggc agg aat gcc gca gcc aac gac aaa gcg tct gac ctg gtc
Ser Asp Gly Arg Asn Ala Ala Ala Asn Asp Lys Ala Ser Asp Leu Val

gct ctg gcc gtc agg gga tgc tgt tcc aac cct atc tgt tac ttt aat
Ala Leu Ala Val Arg Gly Cys Cys Ser Asn Pro Ile Cys Tyr Phe Asn

aat cca cga att tgt cgt gga aga cgc tgatgctcca ggaccctctg
Asn Pro Arg Ile Cys Arg Gly Arg Arg

aaccacgacg t
```

TABLE 92

DNA Sequence (SEQ ID NO:319) and Protein Sequence (SEQ ID NO:320) of Ep1.2

```
tct cat ggc agg aat gcc gca cgc aaa gcg tct gac ctg atc gct ctg
Ser His Gly Arg Asn Ala Ala Arg Lys Ala Ser Asp Leu Ile Ala Leu

acc gtc agg gaa tgc tgt tct cag cct ccc tgt cgc tgg aaa cat cca
Thr Val Arg Glu Cys Cys Ser Gln Pro Pro Cys Arg Trp Lys His Pro

gaa ctt tgt agt tga
Glu Leu Cys Ser
```

TABLE 93

DNA Sequence (SEQ ID NO:321) and Protein Sequence (SEQ ID NO:322) of G1.1

```
tct gat ggc agg aat gac gca gcc aaa gcg ttt gac ctg ata tct tcg
Ser Asp Gly Arg Asn Asp Ala Ala Lys Ala Phe Asp Leu Ile Ser Ser

acc gtc aag aaa gga tgc tgt tcc cat cct gcc tgt gcg ggg aat aat
Thr Val Lys Lys Gly Cys Cys Ser His Pro Ala Cys Ala Gly Asn Asn

caa cat att tgt ggc cga aga cgc tgatgctcca ggaccctctg aaccacgacg
Gln His Ile Cys Gly Arg Arg Arg

t
```

TABLE 94

DNA Sequence (SEQ ID NO:323) and Protein Sequence (SEQ ID NO:324) of G1.3

```
tct gat ggc agg aat gcc gca gcc aac gac caa gcg tct gac ctg atg
Ser Asp Gly Arg Asn Ala Ala Ala Asn Asp Gln Ala Ser Asp Leu Met
```

```
gct gcg acc gtc agg gga tgc tgt gcc gtt cct tcc tgt cgc ctc cgt
Ala Ala Thr Val Arg Gly Cys Cys Ala Val Pro Ser Cys Arg Leu Arg

aat cca gac ctt tgt ggt gga gga cgc tgatgctcca ggaccctctg
Asn Pro Asp Leu Cys Gly Gly Gly Arg

aaccacgacg t
```

TABLE 95

DNA Sequence (SEQ ID NO:325) and Protein Sequence (SEQ ID NO:326) of Im1.3

```
ctt gat gaa agg aat gcc gca gcc gac gac aaa gcg tct gac ctg atc
Leu Asp Glu Arg Asn Ala Ala Ala Asp Asp Lys Ala Ser Asp Leu Ile

gct caa atc gtc agg aga gga tgc tgt tcc cat cct gcc tgt aac gtg
Ala Gln Ile Val Arg Arg Gly Cys Cys Ser His Pro Ala Cys Asn Val

aat aat cca cac att tgt ggt tga
Asn Asn Pro His Ile Cys Gly
```

TABLE 96

DNA Sequence (SEQ ID NO:327) and Protein Sequence (SEQ ID NO:328) of Lv1.2

```
tct gat ggc agg aat act gca gcc aaa gtc aaa tat tct aag acg ccg
Ser Asp Gly Arg Asn Thr Ala Ala Lys Val Lys Tyr Ser Lys Thr Pro

gag gaa tgc tgt ccc aat cct ccc tgt ttc gcg aca aat tcg gat att
Glu Glu Cys Cys Pro Asn Pro Pro Cys Phe Ala Thr Asn Ser Asp Ile

tgt ggc gga aga cgc tgatgctcca ggaccctctg aaccacgacg t
Cys Gly Gly Arg Arg
```

TABLE 97

DNA Sequence (SEQ ID NO:329) and Protein Sequence (SEQ ID NO:330) of Lv1.3

```
tct aat ggc agg aat gcc gca gcc aaa ttc aaa gcg cct gcc ctg atg
Ser Asn Gly Arg Asn Ala Ala Ala Lys Phe Lys Ala Pro Ala Leu Met

aag cgg acc gtc agg gat gct tgc tgt tca gac cct cgc tgt tcc ggg
Lys Arg Thr Val Arg Asp Ala Cys Cys Ser Asp Pro Arg Cys Ser Gly

aaa cat caa gac ctg tgt ggc tgaagacgct gatgctccag gaccctctga
Lys His Gln Asp Leu Cys Gly

accacgacgt
```

TABLE 98

DNA Sequence (SEQ ID NO:331) and Protein Sequence (SEQ ID NO:332) of Lv1.4

```
tct aat ggc agg aat gcc gca gcc aaa ttc aaa gcg cct gcc ctg atg
Ser Asn Gly Arg Asn Ala Ala Ala Lys Phe Lys Ala Pro Ala Leu Met

gag ctg acc gtc agg gaa gat tgc tgt tca gac cct cgc tgt tcc gtg
Glu Leu Thr Val Arg Glu Asp Cys Cys Ser Asp Pro Arg Cys Ser Val
```

```
gga cat caa gac ctg tgt ggc tgaagacgct gatgctccag gaccctctga
Gly His Gln Asp Leu Cys Gly

accacgacgt
```

TABLE 99

DNA Sequence (SEQ ID NO:333) and Protein Sequence (SEQ ID NO:334) of Lv1.6

```
gca ttt gat ggc agg aat gct gca gcc agc gac aaa gcg tcc gag ctg
Ala Phe Asp Gly Arg Asn Ala Ala Ala Ser Asp Lys Ala Ser Glu Leu

atg gct ctg gcc gtc agg gga tgc tgt tcc cat cct gcc tgt gct ggg
Met Ala Leu Ala Val Arg Gly Cys Cys Ser His Pro Ala Cys Ala Gly

agt aat gca cat atc tgt ggc aga aga cgc tgatgctcca ggaccctctg
Ser Asn Ala His Ile Cys Gly Arg Arg Arg

aaccacgacg t
```

TABLE 100

DNA Sequence (SEQ ID NO:335) and Protein Sequence (SEQ ID NO:336) of Lv1.7

```
tct aat ggc agg aat gcc gca gcc aaa ttc aaa gcg cct gcc ctg atg
Ser Asn Gly Arg Asn Ala Ala Ala Lys Phe Lys Ala Pro Ala Leu Met

aag ctg acc gtc agg gag gat tgc tgt tca gac cct cgc tgt tcc gtg
Lys Leu Thr Val Arg Glu Asp Cys Cys Ser Asp Pro Arg Cys Ser Val

gga cat caa gac atg tgt ggc tgaagacgct gatgctccag gaccctctga
Gly His Gln Asp Met Cys Gly

atcacgacgt
```

TABLE 101

DNA Sequence (SEQ ID NO:337) and Protein Sequence (SEQ ID NO:338) of Lv1.8

```
ttt gaa tgc agg aat gct gca ggc aac gac aaa gcg act gac ctg atg
Phe Glu Cys Arg Asn Ala Ala Gly Asn Asp Lys Ala Thr Asp Leu Met

gct ctg act gtc agg gga tgc tgt tcc cat cct gcc tgt gct ggg aat
Ala Leu Thr Val Arg Gly Cys Cys Ser His Pro Ala Cys Ala Gly Asn

aat cca cat atc tgc ggc tgaagacgct gatgctccag gaccctctga
Asn Pro His Ile Cys Gly

accacgacgt
```

TABLE 102

DNA Sequence (SEQ ID NO:339) and Protein Sequence (SEQ ID NO:340) of Lv1.9

```
ttt gat ggc agg aac gcc gca gcc aac aac aaa gcg act gat ctg atg
Phe Asp Gly Arg Asn Ala Ala Ala Asn Asn Lys Ala Thr Asp Leu Met

gct ctg act gtc aga gga tgc tgt ggc aat cct tca tgt agc atc cat
Ala Leu Thr Val Arg Gly Cys Cys Gly Asn Pro Ser Cys Ser Ile His
```

```
att cct tac gtt tgt aat tagagacact gatgctccag gaccctctga
Ile Pro Tyr Val Cys Asn

accacgacgt
```

TABLE 103

DNA Sequence (SEQ ID NO:341) and Protein Sequence (SEQ ID NO:342) of Lv1.10

```
tct aat ggc agg aat gcc gca gcc aaa ttc aaa gcg cct gcc ctg atg
Ser Asn Gly Arg Asn Ala Ala Ala Lys Phe Lys Ala Pro Ala Leu Met

aag cgg acc gac agc gaa gaa tgc tgt tta gac tct cgc tgt gcc ggg
Lys Arg Thr Asp Ser Glu Glu Cys Cys Leu Asp Ser Arg Cys Ala Gly

caa cat caa gac ctg tgt ggc gga aga cgc tgatgctcca ggaccctctg
Gln His Gln Asp Leu Cys Gly Gly Arg Arg

aaccacgacg t
```

TABLE 104

DNA Sequence (SEQ ID NO:343) and Protein Sequence (SEQ ID NO:344) of Mr1.3

```
tct gat ggc agg aat gcc gca gcc aag gac aaa gcg tct gac ctg gtc
Ser Asp Gly Arg Asn Ala Ala Ala Lys Asp Lys Ala Ser Asp Leu Val

gct ctg acc gtc aag gga tgc tgt tct aat cct ccc tgt tac gcg aat
Ala Leu Thr Val Lys Gly Cys Cys Ser Asn Pro Pro Cys Tyr Ala Asn

aat caa gcc tat tgt aat gga aga cgc tga
Asn Gln Ala Tyr Cys Asn Gly Arg Arg
```

TABLE 105

DNA Sequence (SEQ ID NO:345) and Protein Sequence (SEQ ID NO:346) of Mr1.4

```
tct gat ggc agg aat gcc gca gcc aag gac aaa gcg tct gac ctg gtc
Ser Asp Gly Arg Asn Ala Ala Ala Lys Asp Lys Ala Ser Asp Leu Val

gct ctg acc gtc aag gga tgc tgt tct cat cct gcc tgt agc gtg aat
Ala Leu Thr Val Lys Gly Cys Cys Ser His Pro Ala Cys Ser Val Asn

aat cca gac att tgt ggt tga
Asn Pro Asp Ile Cys Gly
```

TABLE 106

DNA Sequence (SEQ ID NO:347) and Protein Sequence (SEQ ID NO:348) of Ms1.1

```
tct gat ggc agg aat gct gca gcc aac aac aaa gtg gct ttg acc atg
Ser Asp Gly Arg Asn Ala Ala Ala Asn Asn Lys Val Ala Leu Thr Met

agg gga aaa tgc tgt atc aat gat gcg tgt cgc tcg aaa cat cca cag
Arg Gly Lys Cys Cys Ile Asn Asp Ala Cys Arg Ser Lys His Pro Gln

tac tgt tct gga aga cgc tgatactcca ggaccctctg aaccacgacg t
Tyr Cys Ser Gly Arg Arg
```

TABLE 107

DNA Sequence (SEQ ID NO:349) and Protein Sequence (SEQ ID NO:350) of Ms1.6

```
tct gat ggc agg aat gct gca gcc aac gac aaa gtg tct gac cag atg
Ser Asp Gly Arg Asn Ala Ala Ala Asn Asp Lys Val Ser Asp Gln Met

gct ctg gtt gtc agg gga tgc tgt tac aat att gcc tgt aga att aat
Ala Leu Val Val Arg Gly Cys Cys Tyr Asn Ile Ala Cys Arg Ile Asn

aat cca cgg tac tgt cgt gga aaa cgc tgatgttcca ggaccctctg
Asn Pro Arg Tyr Cys Arg Gly Lys Arg

aaccacgacg t
```

TABLE 108

DNA Sequence (SEQ ID NO:351) and Protein Sequence (SEQ ID NO:352) of O1.1

```
tctgaaggca ggaatgccgc agccaacgac aaagcgtctg acctgatggc t ctg aac
                                                        Leu Asn

gtc agg gga tgc tgt tcc cat cct gtc tgt cgc ttc aat tat cca aaa
Val Arg Gly Cys Cys Ser His Pro Val Cys Arg Phe Asn Tyr Pro Lys

tat tgt ggt gga aga cgc tgatggtcca ggaccctctg aaccacgacg t
Tyr Cys Gly Gly Arg Arg
```

TABLE 109

DNA Sequence (SEQ ID NO:353) and Protein Sequence (SEQ ID NO:354) of O1.2

```
tctgatggcg ggaatgccgc agcaaaagcg tttgatctaa tcact ctg gcc ctc agg
                                                  Leu Ala Leu Arg

gat gaa tgc tgt gcc agt cct ccc tgt cgt ttg aat aat cca tac gta
Asp Glu Cys Cys Ala Ser Pro Pro Cys Arg Leu Asn Asn Pro Tyr Val

tgt cat tgacgacgct gatgctccag gaccctctga accacgacgt
Cys His
```

TABLE 110

DNA Sequence (SEQ ID NO:355) and Protein Sequence (SEQ ID NO:356) of O1.4

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ccc act tca gat cgt gca tct gat agg agg aat gcc gca gcc aaa gcg
Pro Thr Ser Asp Arg Ala Ser Asp Arg Arg Asn Ala Ala Ala Lys Ala

ttt gac ctg aga tat tcg acc gcc aag aga gga tgc tgt tcc aat cct
Phe Asp Leu Arg Tyr Ser Thr Ala Lys Arg Gly Cys Cys Ser Asn Pro

gtc tgt tgg cag aat aat gca gaa tac tgt cgt gaa agt ggc
Val Cys Trp Gln Asn Asn Ala Glu Tyr Cys Arg Glu Ser Gly

taatgctcca ggaccctctg aaccacgacg t
```

TABLE 111

DNA Sequence (SEQ ID NO:357) and Protein Sequence (SEQ ID NO:358) of O1.7

```
atg ttc acc gtg ttt ctg ttg gtt gtc ttg gca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ala Thr Thr Val Val Ser

ttc act tca gat cgt gca tct gat ggc ggg aat gtc gca gcg tct cac
Phe Thr Ser Asp Arg Ala Ser Asp Gly Gly Asn Val Ala Ala Ser His

ctg atc gct ctg acc atc aag gga tgc tgt tct cac cct ccc tgt gcc
Leu Ile Ala Leu Thr Ile Lys Gly Cys Cys Ser His Pro Pro Cys Ala

cag aat aat caa gac tat tgt ggt tgacgacgct gatgctccag gaccctctga
Gln Asn Asn Gln Asp Tyr Cys Gly

accacgacgt
```

TABLE 112

DNA Sequence (SEQ ID NO:359) and Protein Sequence (SEQ ID NO:360) of O1.8

```
atg ttc acc gtg ttt ctg ttg gtt gtc tta tca acc acc gtc gtt tcc
Met Phe Thr Val Phe Leu Leu Val Val Leu Ser Thr Thr Val Val Ser

tcc act tca gat cgt gca tct gat agg agg aat gcc gca gcc aaa gcg
Ser Thr Ser Asp Arg Ala Ser Asp Arg Arg Asn Ala Ala Ala Lys Ala

tct gac ctg atg tat tcg acc gtc aag aaa gga tgt tgt tcc cat cct
Ser Asp Leu Met Tyr Ser Thr Val Lys Lys Gly Cys Cys Ser His Pro

gcc tgt tcg ggg aat aat cga gaa tat tgt cgt gaa agt ggc
Ala Cys Ser Gly Asn Asn Arg Glu Tyr Cys Arg Glu Ser Gly

taatgctcca ggaccctctg aaccacgacg t
```

TABLE 113

DNA Sequence (SEQ ID NO:361) and Protein Sequence (SEQ ID NO:362) of Om1.2

```
tttgatggca ggaatgcctc agccgacagc aaagtggctg cccggatcgc t cag atc
                                                        Gln Ile

gac agg gat cca tgc tgt tcc tat cct gac tgt ggc gcg aat cat cca
Asp Arg Asp Pro Cys Cys Ser Tyr Pro Asp Cys Gly Ala Asn His Pro

gag att tgt ggt gga aaa cgc tgatgctcca ggaccctctg aaccacgacg t
Glu Ile Cys Gly Gly Lys Arg
```

TABLE 114

DNA Sequence (SEQ ID NO:363) and Protein Sequence (SEQ ID NO:364) of Om1.3

```
tctcatggca ggaatgccgc acgct ctg acc gtc agg gaa tgc tgt tct cag
                           Leu Thr Val Arg Glu Cys Cys Ser Gln

cct cct tgt cgc tgg aaa cat cca gaa ctt tgt agt tgaagacgct
Pro Pro Cys Arg Trp Lys His Pro Glu Leu Cys Ser
```

gatgctccag gaccctctga accacgacgt

TABLE 115

DNA Sequence (SEQ ID NO:365) and Protein Sequence (SEQ ID NO:366) of Om1.4

```
tttgatggca ggaatgctgc agccagcgac aaagcgtctg agctgatggc t ctg gcc
                                                        Leu Ala

gtc agg gga tgc tgt tcc cat cct gcc tgt gct ggg aat aat cca cat
Val Arg Gly Cys Cys Ser His Pro Ala Cys Ala Gly Asn Asn Pro His

atc tgt ggc aga aga cgc tgatgctcca ggaccctctg aaccacgacg t
Ile Cys Gly Arg Arg Arg
```

TABLE 116

DNA Sequence (SEQ ID NO:367) and Protein Sequence (SEQ ID NO:368) of Om1.5

```
tctggtgtca ggaaagacgc agcgcctggc ctgatcgct ctg acc atc aag gga
                                          Leu Thr Ile Lys Gly

tgc tgt tct gat cct agc tgt aac gtg aat aat cca gac tat tgt ggt
Cys Cys Ser Asp Pro Ser Cys Asn Val Asn Asn Pro Asp Tyr Cys Gly

tgacgacgct gatgctccag gaccctctga accacgacgt
```

TABLE 117

DNA Sequence (SEQ ID NO:369) and Protein Sequence (SEQ ID NO:370) of Om1.6

```
tctaatggca ggaatgccgc agccaaattc aaagcgcctg ccctgatgga g ctg acc  57
                                                        Leu Thr

gtc agg gaa gaa tgc tgt tca gac cct cgc tgt tcc gtg gga cat caa   105
Val Arg Glu Glu Cys Cys Ser Asp Pro Arg Cys Ser Val Gly His Gln

gat atg tgt cgg tgaagcacgt gatgctccag gaccctctga accacgacgt       157
Asp Met Cys Arg
```

TABLE 118

DNA Sequence (SEQ ID NO:371) and Protein Sequence (SEQ ID NO:372) of P1.4

```
act gat ggc agg aat gct gca gcc ata gcg ctt gac ctg atc gct ccg
Thr Asp Gly Arg Asn Ala Ala Ala Ile Ala Leu Asp Leu Ile Ala Pro

gcc gtc agg gga gga tgc tgt tcc aat cct gcc tgt tta gtg aat cat
Ala Val Arg Gly Gly Cys Cys Ser Asn Pro Ala Cys Leu Val Asn His

cta gaa atg tgt ggt aaa aga cgc tgatgcccca ggaccctctg aaccacgacg
Leu Glu Met Cys Gly Lys Arg Arg

t
```

TABLE 119

DNA Sequence (SEQ ID NO:373) and Protein Sequence (SEQ ID NO:374) of P1.5

```
tct gat ggc agg gat gcc gca gcc aac gac aaa gcg tct gac ctg atc
Ser Asp Gly Arg Asp Ala Ala Ala Asn Asp Lys Ala Ser Asp Leu Ile

gct ctg acc gcc agg aga gat cca tgc tgt ttc aat cct gcc tgt aac
Ala Leu Thr Ala Arg Arg Asp Pro Cys Cys Phe Asn Pro Ala Cys Asn

gtg aat aat cca cag att tgt ggt tgaagacgct gatgctccag gaccctctga
Val Asn Asn Pro Gln Ile Cys Gly

accacgacgt
```

TABLE 120

DNA Sequence (SEQ ID NO:375) and Protein Sequence (SEQ ID NO:376) of P1.6

```
tct gat ggc agg gat gct gag aaa aca ggc ttt gac acg acc att gtg
Ser Asp Gly Arg Asp Ala Glu Lys Thr Gly Phe Asp Thr Thr Ile Val

ccg gaa gac tgc tgt tcg gat cct tcc tgt tgg agg ctg cat agt tta
Pro Glu Asp Cys Cys Ser Asp Pro Ser Cys Trp Arg Leu His Ser Leu

gct tgt act gga att gta aac cgc tgatgctcca ggaccctctg aaccacgacg
Ala Cys Thr Gly Ile Val Asn Arg

t
```

TABLE 121

DNA Sequence (SEQ ID NO:377) and Protein Sequence (SEQ ID NO:378) of P1.8

```
act gat ggc agg agt gct gca gcc ata gcg ttt gcc ctg atc gct ccg
Thr Asp Gly Arg Ser Ala Ala Ala Ile Ala Phe Ala Leu Ile Ala Pro

acc gtc tgc tgt act aat cct gcc tgt ctc gtg aat aat ata cgc ttt
Thr Val Cys Cys Thr Asn Pro Ala Cys Leu Val Asn Asn Ile Arg Phe

tgt ggt gga aga cgc tgatgcccca ggaccctctg aaccacgacg t
Cys Gly Gly Arg Arg
```

TABLE 122

DNA Sequence (SEQ ID NO:379) and Protein Sequence (SEQ ID NO:380) of Rg1.1

```
tct gat gga aga aat gcc gca agc gac gcc aaa gcg ttt ccc cgg atc
Ser Asp Gly Arg Asn Ala Ala Ser Asp Ala Lys Ala Phe Pro Arg Ile

gct cca atc gtc agg gac gaa tgc tgt agc gat cct agg tgt cac ggg
Ala Pro Ile Val Arg Asp Glu Cys Cys Ser Asp Pro Arg Cys His Gly

aat aat cgg gac cac tgt gct tgaagacgct gctgctccag gaccctctga
Asn Asn Arg Asp His Cys Ala

accacgacgt
```

TABLE 123

DNA Sequence (SEQ ID NO:381) and Protein Sequence (SEQ ID NO:382) of Rg1.3

```
tct gat ggc agg aat acc gcg gcc gac gaa aaa gcg tcc gac ctg atc
Ser Asp Gly Arg Asn Thr Ala Ala Asp Glu Lys Ala Ser Asp Leu Ile

tct caa act gtc aag aga gat tgc tgt tcc cat cct ctc tgt aga tta
Ser Gln Thr Val Lys Arg Asp Cys Cys Ser His Pro Leu Cys Arg Leu

ttt gtt cca gga ctt tgt att tgaagacgct gctgctccag gaccctctga
Phe Val Pro Gly Leu Cys Ile

accacgact
```

TABLE 124

DNA Sequence (SEQ ID NO:383) and Protein Sequence (SEQ ID NO:384) of Rg1.4

```
tct gat ggc agg aat gcc gca gcc gac aac aaa gcg tct gac cta atc
Ser Asp Gly Arg Asn Ala Ala Ala Asp Asn Lys Ala Ser Asp Leu Ile

gct caa atc gtc agg aga gga tgc tgt tcc cat cct gtc tgt aaa gtg
Ala Gln Ile Val Arg Arg Gly Cys Cys Ser His Pro Val Cys Lys Val

agg tat cca gac ctg tgt cgt tgaagacgct gctgctccag gaccctctga
Arg Tyr Pro Asp Leu Cys Arg

accacgacgt
```

TABLE 125

DNA Sequence (SEQ ID NO:385) and Protein Sequence (SEQ ID NO:386) of Rg1.5

```
tct gat ggc agg aat gcc gca gcc gac aac aga gcg tct gac cta atc
Ser Asp Gly Arg Asn Ala Ala Ala Asp Asn Arg Ala Ser Asp Leu Ile

gct caa atc gtc agg aga gga tgc tgt tcc cat cct gcc tgt aat gtg
Ala Gln Ile Val Arg Arg Gly Cys Cys Ser His Pro Ala Cys Asn Val

aat aat cca cac att tgt ggt tgaagacgct gctgctccag gaccctctga
Asn Asn Pro His Ile Cys Gly

accacgacgt
```

TABLE 126

DNA Sequence (SEQ ID NO:387) and Protein Sequence (SEQ ID NO:388) of Rg1.8

```
tct gat ggc agg aat gcc gca gcc gac aac aaa ccg tct gac cta atc
Ser Asp Gly Arg Asn Ala Ala Ala Asp Asn Lys Pro Ser Asp Leu Ile

gct caa atc gtc agg aga gga tgc tgt tcg cat cct gtc tgt aaa gtg
Ala Gln Ile Val Arg Arg Gly Cys Cys Ser His Pro Val Cys Lys Val

agg tat tca gac atg tgt ggt tgaagacgct gctgctccag gaccctctga
Arg Tyr Ser Asp Met Cys Gly

accacgacgt
```

TABLE 127

DNA Sequence (SEQ ID NO:389) and Protein Sequence (SEQ ID NO:390) of Sm1.4

```
tct gat ggc agg aat gca gag cga cga caa agc gtc tgt cct ggt cgc
Ser Asp Gly Arg Asn Ala Glu Arg Arg Gln Ser Val Cys Pro Gly Arg

tct ggc ccc agg gga gga tgt tgt tcc cac cct gcc tgt aag gtg cat
Ser Gly Pro Arg Gly Gly Cys Cys Ser His Pro Ala Cys Lys Val His

ttt cca cac agt tgt ggt tgacgacgct gatgctccag gaccctctga
Phe Pro His Ser Cys Gly

accacgacgt
```

TABLE 128

DNA Sequence (SEQ ID NO:391) and Protein Sequence (SEQ ID NO:392) of Sm1.5

```
tct gat ggc agg aat gcc gca gcc agc gac aga gcg tct gac gcg gcc
Ser Asp Gly Arg Asn Ala Ala Ala Ser Asp Arg Ala Ser Asp Ala Ala

cac cag gta tgc tgt tcc aac cct gtc tgt cac gtg gat cat cca gaa
His Gln Val Cys Cys Ser Asn Pro Val Cys His Val Asp His Pro Glu

ctt tgt cgt aga aga cgc tgatgctcca ggaccctctg aaccacgacg t
Leu Cys Arg Arg Arg Arg
```

TABLE 129

DNA Sequence (SEQ ID NO:393) and Protein Sequence (SEQ ID NO:394) of S1.5

```
tct gat ggc agg aat gcc gcg gcc aac gac aaa gcg tct gac ctg gtc
Ser Asp Gly Arg Asn Ala Ala Ala Asn Asp Lys Ala Ser Asp Leu Val

gct ccg gcc atc agg gga tgc tgt tcc cac cct gtc tgt aac ttg agt
Ala Pro Ala Ile Arg Gly Cys Cys Ser His Pro Val Cys Asn Leu Ser

aat cca caa att tgt cgt gga aga cgc tgatgctcca ggaccctctg
Asn Pro Gln Ile Cys Arg Gly Arg Arg

aaccacgacg t
```

TABLE 130

DNA Sequence (SEQ ID NO:395) and Protein Sequence (SEQ ID NO:396) of Tx1.5

```
ttt cat ggc agg aat gcc gca gcc aaa gcg tct ggc ctg gtc ggt ctg
Phe His Gly Arg Asn Ala Ala Ala Lys Ala Ser Gly Leu Val Gly Leu

acc gac aag agg caa gaa tgc tgt tct cat cct gcc tgt aac gta gat
Thr Asp Lys Arg Gln Glu Cys Cys Ser His Pro Ala Cys Asn Val Asp

cat cca gaa att tgt cgt tga
His Pro Glu Ile Cys Arg
```

TABLE 131

DNA Sequence (SEQ ID NO:397) and Protein Sequence (SEQ ID NO:398) of T1.1

```
act gat ggc agg agt gct gca gcc ata gcg ttt gcc ctg atc gct ccg
Thr Asp Gly Arg Ser Ala Ala Ala Ile Ala Phe Ala Leu Ile Ala Pro

acc gtc tgg gaa gga tgc tgt tct aat cct gcc tgt ctc gtg aat cat
Thr Val Trp Glu Gly Cys Cys Ser Asn Pro Ala Cys Leu Val Asn His

ata cgc ttt tgt ggt gga aga cgc tgatgcccca ggaccctctg aaccacgacg
Ile Arg Phe Cys Gly Gly Arg Arg

t
```

TABLE 132

DNA Sequence (SEQ ID NO:399) and Protein Sequence (SEQ ID NO:400) of Vr1.3

```
tct aat ggc atg aat gcc gca gcc atc agg aaa gcg tct gcc ctg gtg
Ser Asn Gly Met Asn Ala Ala Ala Ile Arg Lys Ala Ser Ala Leu Val

gct cag atc gcc cat cga gac tgc tgt gac gat cct gcc tgc acc gtg
Ala Gln Ile Ala His Arg Asp Cys Cys Asp Asp Pro Ala Cys Thr Val

aat aat cca ggc ctt tgc act tgaagatgct gctgccccag gaccctctga
Asn Asn Pro Gly Leu Cys Thr

accacgacgt
```

TABLE 133

DNA Sequence (SEQ ID NO:401) and Protein Sequence (SEQ ID NO:402) of G1.2

```
tct gat ggc ggg aat gcc gca gca aaa gag tct gac gtg atc gct ctg
Ser Asp Gly Gly Asn Ala Ala Ala Lys Glu Ser Asp Val Ile Ala Leu

acc gtc tgg aaa tgc tgt acc att cct tcc tgt tat gag aaa aaa aaa
Thr Val Trp Lys Cys Cys Thr Ile Pro Ser Cys Tyr Glu Lys Lys Lys

att aaa gca tgt gtc ttt tgacgacgct gatgctccag gaccctctga
Ile Lys Ala Cys Val Phe

accacgacgt
```

TABLE 134

DNA Sequence (SEQ ID NO:403) and Protein Sequence (SEQ ID NO:404) of Rg1.12

```
tct gat ggc gca gtc gac gac aaa gcg ttg gat cga atc gct gaa atc
Ser Asp Gly Ala Val Asp Asp Lys Ala Leu Asp Arg Ile Ala Glu Ile

gtc agg aga gga tgc tgt ggc aat cct gcc tgt agc ggc tcc tcg aaa
Val Arg Arg Gly Cys Cys Gly Asn Pro Ala Cys Ser Gly Ser Ser Lys

gat gca ccc tct tgt ggt tgaagacgct gctgctccag gaccctctga
Asp Ala Pro Ser Cys Gly

accacgacgt
```

It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

LIST OF REFERENCES

Barnay, G. et al. (2000). *J. Med. Chem.*

Bitan, G. et al. (1997). *J. Peptide Res.* **49**:421-426.

Blount, K. et al. (1992). *Toxicon* **30**:835-842.

Bodansky et al. (1966). *Chem. Ind.* **38**:1597-98.

Cartier, G.E. et al. (1996). *J. Biol. Chem.* **271**:7522-7528.

Cruz, L.J. at al. (1976). *Verliger* **18**:302-308.

Cruz, L.J. et al. (1987). *J. Biol. Chem.* **260**:9280-9288.

Fainzilber, M. et al. (1994). *Biochemistry* **33**:9523-9529.

Gray, W.R. et al. (1981). *J.Biol. Chem.* **256**:4734-4740.

Haack, J.A. et al. (1990). *J. Biol. Chem.* **265**:6025-6029.

Horiki, K. et al. (1978). *Chemistry Letters* 165-68.

~~Hubby, V. et al. (1994). *Reactive Polymers* **22**:231-241.~~

Jacobsen, R. et al. (1997). *J. Biol. Chem.* **272**:22531-22537.

Johnson, D.S. et al. (1995). *Mol. Pharmacol.* **48**:194-199.

Kapoor (1970). *J. Pharm. Sci.* **59**:1-27.

Kornreich, W.D. et al. (1986). U.S. Patent No. 4,569,967.

Luo, S. et al. (1998). *J. Neurosci.* **18**:8571-8679.

Marshall, I.G. and Harvey, A.L. (1990). *Toxicon* **28**:231-234.

Martinez, J.S. et al. (1995). *Biochem.* **34**:14519-14526.

McIntosh, J.M. et al. (1982). *Arch. Biochem. Biophys.* **218**:329-334.

Mena, E.E. et al. (1990). *Neurosci. Lett.* **118**:241-244.

Methoden der Organischen Chemie (Houben-Weyl): Synthese von Peptiden, E. Wunsch (Ed.), Georg Thieme Verlag, Stuttgart, Ger. (1974).

Myers, R.A. et al. (1991). *Biochemistry* **30**:9370-9377.

Nishiuchi, Y. et al. (1993). *Int. J. Pept. Protein Res.* **42**:533-538.

Nowak, L. et al. (1984). *Nature* **307**:462-465.

Olivera, B.M. et al. (1984). U.S. Patent 4,447,356.

Olivera, B.M. et al. (1985). *Science* **230**:1338-1343.

Olivera, B.M. et al. (1996). U.S. Patent 5,514,774.

Rivier, J.R. et al. (1978). *Biopolymers* **17**:1927-38.

Rivier, J.R. et al. (1987). *Biochem.* **26**:8508-8512.

Sambrook, J. et al. (1989). *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Schroder & Lubke (1965). *The Peptides* **1**:72-75, Academic Press, NY.

Shon, K.-J. et al. (1994). *Biochemistry* **33**:11420-11425.

Stewart and Young, *Solid-Phase Peptide Synthesis*, Freeman & Co., San Francisco, CA (1969).

Vale et al. (1978). U.S. Patent 4,105,603.

Van de Steen, P. et al. (1998). *Critical Rev. in Biochem. and Mol. Biol.* **33**:151-208.

Zafaralla, G.C. et al. (1988). *Biochemistry* **27**:7102-7105.

Zhou L.M., et al. (1996). *J. Neurochem.* **66**:620-628.

U.S. Patent No. 3,972,859.

U.S. Patent No. 3,842,067.

U.S. Patent No. 3,862,925.

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